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(54) **COMPOUNDS CONTAINING S-N-VALERYL-N-{[2'-(1H-TETRAZOLE-5-YL)-BIPHENYL-4-YL]-METHYL)-VALINE AND (2R,4S)-5-BIPHENYL-4-YL-4-(3-CARBOXY-PROPIONYLAMINO)-2-METHYL-PENTANOIC ACID ETHYL ESTER MOIETIES AND CATIONS**

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(58) **Field of Classification Search**

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(57) **ABSTRACT**

A method for treatment of a cardiovascular or renal condition or disease with a specific combination, linked pro-drug or a compound of an angiotensin receptor antagonist and a NEPi.

15 Claims, 1 Drawing Sheet

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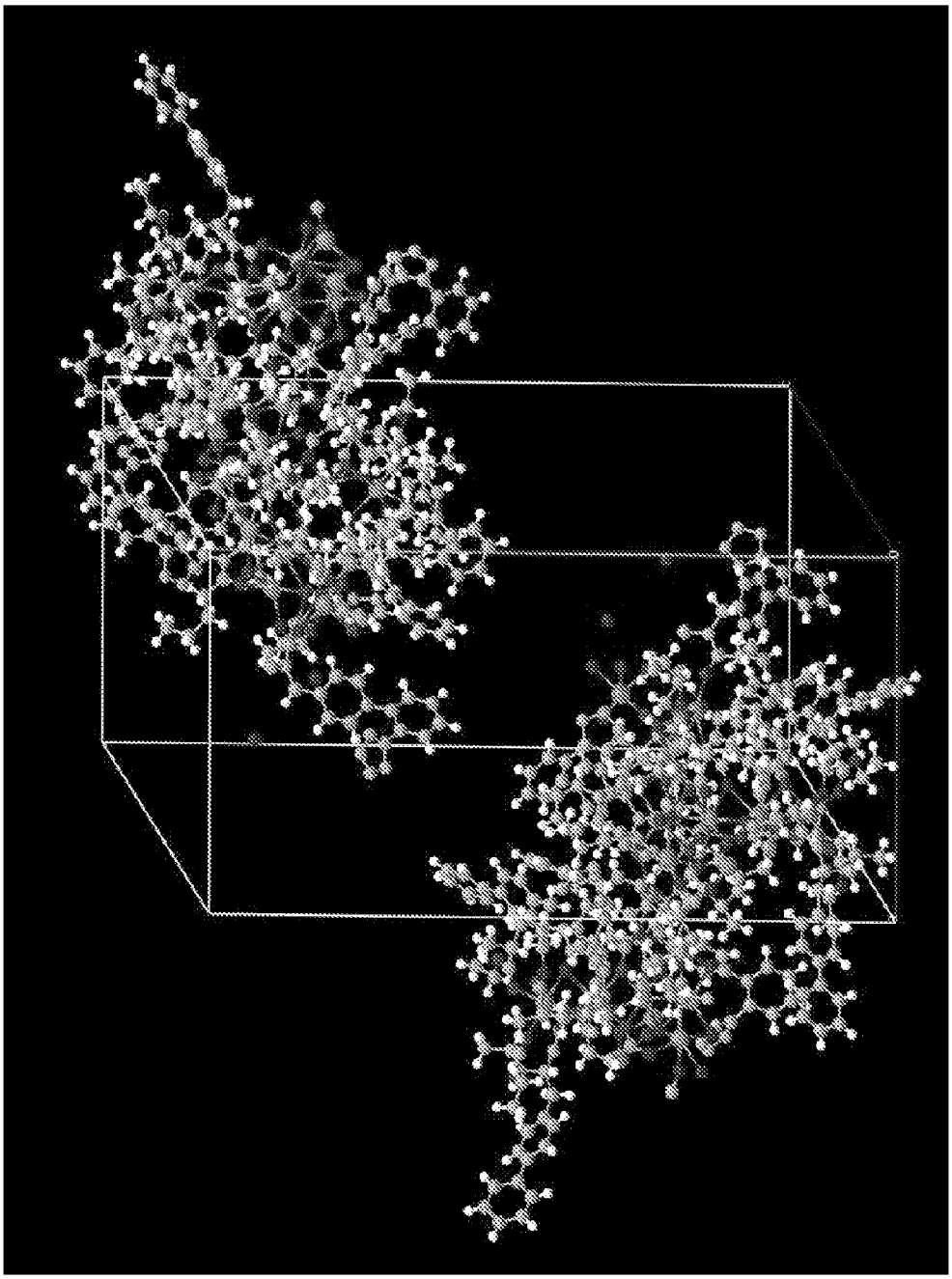
unit cell of the supramolecular complex of trisodium [3-((1*S*,3*R*)-1-biphenyl-4-ylmethyl-3-ethoxycarbonyl-1-butylcarbamoyl)propionate-(*S*)-3'-methyl-2'-(pentanoyl{2''-(tetrazol-5-ylate)biphenyl-4'-ylmethyl}amino)butyrate] hemipentahydrate comprising two asymmetric units



COMPOUNDS CONTAINING S-N-VALERYL-N-{[2'-(1H-TETRAZOLE-5-YL)-BIPHENYL-4-YL]-METHYL)-VALINE AND (2R,4S)-5-BIPHENYL-4-YL-4-(3-CARBOXY-PROPIONYLAMINO)-2-METHYL-PENTANOIC ACID ETHYL ESTER MOIETIES AND CATIONS

BACKGROUND OF THE INVENTION

1. Field of the Invention

The present invention is directed to dual-acting compounds and combinations of angiotensin receptor blockers and neutral endopeptidase inhibitors, in particular a dual acting molecule wherein the angiotensin receptor blocker and neutral endopeptidase inhibitor are linked via non-covalent bonding, or supramolecular complexes of angiotensin receptor blockers and neutral endopeptidase inhibitors, also described as linked pro-drugs, such as mixed salts or co-crystals, as well as to pharmaceutical combinations containing such a dual-acting compound or combination, methods of preparing such dual-acting compounds and methods of treating a subject with such a dual-acting compound or combination. Specifically, the invention is directed to a dual acting compound or supramolecular complex of two active agents having the same or different modes of action in one molecule.

2. Related Background Art

Angiotensin II is a hormone that causes blood vessels to constrict. This, in turn, can result in high blood pressure and strain on the heart. It is known that angiotensin II interacts with specific receptors on the surface of target cells. Two receptor subtypes for angiotensin II, namely AT1 and AT2, have been identified thus far. In recent times, great efforts have been made to identify substances that bind to the AT1 receptor. Angiotensin receptor blockers (ARBs, angiotensin II antagonists) are now known to prevent angiotensin II from binding to its receptors in the walls of blood vessels, thereby resulting in lower blood pressure. Because of the inhibition of the AT1 receptor, such antagonists can be used, therefore, as anti-hypertensives or for the treatment of congestive heart failure, among other indications.

Neutral endopeptidase (EC 3.4.24.11; enkephalinase; atriopeptidase; NEP) is a zinc-containing metalloprotease that cleaves a variety of peptide substrates on the amino side of hydrophobic residues [see *Pharmacol Rev*, Vol. 45, p. 87 (1993)]. Substrates for this enzyme include, but are not limited to, atrial natriuretic peptide (ANP, also known as ANF), brain natriuretic peptide (BNP), met- and leu-enkephalin, bradykinin, neurokinin A, endothelin-1 and substance P. ANP is a potent vasorelaxant and natriuretic agent [see *J Hypertens*, Vol. 19, p. 1923 (2001)]. Infusion of ANP in normal subjects resulted in a reproducible, marked enhancement of natriuresis and diuresis, including increases in fractional excretion of sodium, urinary flow rate and glomerular filtration rate [see *J Clin Pharmacol*, Vol. 27, p. 927 (1987)]. However, ANP has a short half-life in circulation, and NEP in kidney cortex membranes has been shown to be the major enzyme responsible for degrading this peptide [see *Peptides*, Vol. 9, p. 173 (1988)]. Thus, inhibitors of NEP (neutral endopeptidase inhibitors, NEPi) should increase plasma levels of ANP and, hence, are expected to induce natriuretic and diuretic effects.

While substances, such as angiotensin receptor blockers and neutral endopeptidase inhibitors may be useful in the control of hypertension, essential hypertension is a polygenic disease and is not always controlled adequately by monotherapy. Approximately 333 million adults in economically developed countries and about 65 million Americans (1 in 3 adults) had high blood pressure in 2000 [see *Lancet*, Vol. 365, p. 217 (2005); and *Hypertension*, Vol. 44, p. 398 (2004)]. Prolonged and uncontrolled hypertensive vascular disease ultimately leads to a variety of pathological changes in target organs, such as the heart and kidney. Sustained hypertension can lead as well to an increased occurrence of stroke. Therefore, there is a strong need to evaluate the efficacy of anti-hypertensive therapy, an examination of additional cardiovascular endpoints, beyond those of blood pressure lowering, to get further insight into the benefits of combined treatment.

The nature of hypertensive vascular diseases is multifactorial. Under certain circumstances, drugs with different mechanisms of action have been combined. However, just considering any combination of drugs having different modes of action does not necessarily lead to combinations with advantageous effects. Accordingly, there is a need for efficacious combination therapy which does not have deleterious side effects.

SUMMARY OF THE INVENTION

In a first aspect, the present invention is directed to a dual-acting compound, such as a supramolecular complex, comprising:

(a) an angiotensin receptor antagonist;

(b) a neutral endopeptidase inhibitor (NEPi); and optionally

(c) a pharmaceutically acceptable cation.

The present invention is also directed to a dual-acting compound, such as a supramolecular complex, obtainable by:

(i) dissolving an angiotensin receptor antagonist and a neutral endopeptidase inhibitor (NEPi) in a suitable solvent;

(ii) dissolving a basic compound of Cat in a suitable solvent, wherein Cat is a cation;

(iii) combining the solutions obtained in steps (i) and (ii);

(iv) precipitation of the solid, and drying same to obtain the dual-acting compound; or alternatively

obtaining the dual-acting compound by exchanging the solvent(s) employed in steps (i) and (ii) by

(iva) evaporating the resulting solution to dryness;

(va) re-dissolving the solid in a suitable solvent;

(via) precipitation of the solid and drying same to obtain the dual-acting compound.

The present invention is also directed to linked pro-drugs comprising:

(a) an angiotensin receptor antagonist or a pharmaceutically acceptable salt thereof; and

(b) a NEPi or a pharmaceutically acceptable salt thereof, wherein the angiotensin receptor antagonist or a pharmaceutically acceptable salt thereof and the NEPi or a pharmaceutically acceptable salt thereof are linked by a linking moiety.

The present invention is also directed to a combination comprising:

(a) a pharmaceutically acceptable salt of an angiotensin receptor antagonist; and

(b) a pharmaceutically acceptable salt of a neutral endopeptidase inhibitor (NEPi);

wherein the pharmaceutically acceptable salt of the angiotensin receptor antagonist and the NEPi is the same and is selected from a salt of Na, K or NH_4.

In preferred embodiments, the angiotensin receptor antagonist and NEPi have acidic groups which facilitate formation of the dual acting compound, such as the supramolecular complex of the present invention.

Preferably, the angiotensin receptor antagonist is selected from the group consisting of valsartan, losartan, irbesartan, telmisartan, eprosartan, candesartan, olmesartan, saprisartan, tasosartan, elisartan and combinations thereof.

In preferred embodiments, the NEPi is selected from the group consisting of: SQ 28,603; N—[N-[1(S)-carboxyl-3-phenylpropyl]-(S)-phenylalanyl]-(S)-isoserine; N—[N-[((1S)-carboxy-2-phenypethyl]-(S)-phenylalanyl]-β-alanine; N-[2(S)-mercaptomethyl-3-(2-methylphenyl)-propionyl]methionine; (cis-4-[[[1-[2-carboxy-3-(2-methoxyethoxy)propyl]-cyclopentyl]carbonyl]amino]-cyclohexanecarboxylic acid); thiorphan; retro-thiorphan; phosphoramidon; SQ 29072; N-(3-carboxy-1-oxopropyl)-(4S)-p-phenylphenylmethyl)-4-amino-2R-methylbutanoic acid ethyl ester; (S)-cis-4-[1-[2-(5-indanyloxycarbonyl)-3-(2-methoxyethoxy)propyl]-1-cyclopentanecarboxamido]-1-cyclohexanecarboxylic acid; 3-(1-[6-endo-hydroxymethyl-bicyclo[2,2,1]heptane-2-exo-carbamoyl]cyclopentyl)-2-(2-methoxyethyl)propanoic acid; N-(1-(3-(N-t-butoxycarbonyl-(S)-prolylamino)-2(S)-t-butoxy-carbonylpropyl)cyclopentanecarbonyl)-O-benzyl-(S)-serine methyl ester; 4-[[2-(mercaptomethyl)-1-oxo-3-phenylpropyl]amino]benzoic acid; 3-[1-(cis-4-carboxycarbonyl-cis-3-butylcyclohexyl-r-1-carbamoyl)cyclopentyl]-2S-(2-methoxyethoxymethyl)propanoic acid; N-((2S)-2-(4-biphenylmethyl)-4-carboxy-5-phenoxyvaleryl)glycine; N-(1-(N-hydroxycarbamoylmethyl)-1-cyclopentanecarbonyl)-L-phenylalanine; (S)-(2-biphenyl-4-yl)-1-(1H-tetrazol-5-yl)ethylamino)methylphosphonic acid; (S)-5-(N-(2-(phosphonomethylamino)-3-(4-biphenyl)propionyl)-2-aminoethyl)tetrazole; β-alanine; 3-[1,1'-biphenyl]-4-yl-N-[diphenoxyphosphinyl)methyl]-L-alanyl; N-(2-carboxy-4-thienyl)-3-mercapto-2-benzylpropanamide; 2-(2-mercaptomethyl-3-phenylpropionamido)thiazol-4-ylcarboxylic acid; (L)-(1-((2,2-dimethyl-1,3-dioxolan-4-yl)-methoxy)carbonyl)-2-phenylethyl)-L-phenylalanyl)-β-alanine; N—[N-[(L)-[1-[(2,2-dimethyl-1,3-dioxolan-4-yl)-methoxy]carbonyl]-2-phenylethyl]-L-phenylalanyl]-(R)-alanine; N—[N-[(L)-1-carboxy-2-phenylethyl]-L-phenylalanyl]-(R)-alanine; N-[2-acetylthiomethyl-3-(2-methyl-phenyl)propionyl]-methionine ethyl ester; N-[2-mercaptomethyl-3-(2-methylphenyl)propionyl]-methionine; N-[2(S)-mercaptomethyl-3-(2-methylphenyl)propanoyl]-(S)-isoserine; N—(S)-[3-mercapto-2-(2-methylphenyl)propionyl]-(S)-2-methoxy-(R)-alanine; N-[1-[[1(S)-benzyloxy-carbonyl-3-phenylpropyl]amino]cyclopentylcarbonyl]-(S)-isoserine; N-[1-[[1(S)-carbonyl-3-phenylpropyl]amino]-cyclopentylcarbonyl]-(S)-isoserine; 1,1'-[dithiobis-[2(S)-(2-methylbenzyl)-1-oxo-3,1-propanediyl]]-bis-(S)-isoserine; 1,1'-[dithiobis-[2(S)-(2-methylbenzyl)-1-oxo-3,1-propanediyl]]-bis-(S)-methionine; N-(3-phenyl-2-(mercaptomethyl)-propionyl)-(S)-4-(methylmercapto)methionine; N-[2-acetylthiomethyl-3-phenyl-propionyl]-3-aminobenzoic acid; N-[2-mercaptomethyl-3-phenyl-propionyl]-3-aminobenzoic acid; N-[1-(2-carboxy-4-phenylbutyl)-cyclopentane-carbonyl]-(S)-isoserine; N-[1-(acetylthiomethyl)cyclopentane-carbonyl]-(S)-methionine ethyl ester; 3(S)-[2-(acetylthiomethyl)-3-phenyl-propionyl]amino-ϵ-caprolactam; N-(2-acetylthiomethyl-3-(2-methylphenyl)propionyl)-methionine ethyl ester; and combinations thereof. Preferably, the dual-acting compound or combination, in particular the supramolecular complex, is a mixed salt or a co-crystal. It is also preferred that the linked pro-drug is a mixed salt or a co-crystal.

In a second aspect, the present invention is directed to pharmaceutical composition comprising

(a) the aforementioned dual-acting compound or combination, such as the aforementioned complex; and

(b) at least one pharmaceutically acceptable additive.

The present invention is also directed to pharmaceutical compositions comprising a linked pro-drug comprising:

(a) an angiotensin receptor antagonist or a pharmaceutically acceptable salt thereof;

(b) a NEPi or a pharmaceutically acceptable salt thereof,

wherein the angiotensin receptor antagonist or a pharmaceutically acceptable salt thereof and the NEPi or a pharmaceutically acceptable salt thereof are linked by a linking moiety; and

(c) at least one pharmaceutically acceptable additive.

In a third aspect, the present invention is directed to a method of preparing a dual-acting compound, in particular a supramolecular complex, comprising

(a) an angiotensin receptor antagonist;

(b) a neutral endopeptidase inhibitor (NEPi); and optionally

(c) a pharmaceutically acceptable cation selected from the group consisting of Na, K and NH_4;

said method comprising the steps of:

(i) dissolving an angiotensin receptor antagonist and a neutral endopeptidase inhibitor (NEPi) in a suitable solvent;

(ii) dissolving a basic compound of Cat in a suitable solvent, wherein Cat is a cation;

(iii) combining the solutions obtained in steps (i) and (ii);

(iv) precipitation of the solid, and drying same to obtain the dual-acting compound; or alternatively

obtaining the dual-acting compound by exchanging the solvent(s) employed in steps (i) and (ii) by

(iva) evaporating the resulting solution to dryness;

(va) re-dissolving the solid in a suitable solvent;

(via) precipitation of the solid and drying same to obtain the dual-acting compound.

The present invention is also directed to a method of making a linked pro-drug comprising:

(a) an angiotensin receptor antagonist or a pharmaceutically acceptable salt thereof;

(b) a NEPi or a pharmaceutically acceptable salt thereof, wherein the angiotensin receptor antagonist or a pharmaceutically acceptable salt thereof and the NEPi or a pharmaceutically acceptable salt thereof are linked by a linking moiety; and

comprising adding a linking moiety and a solvent to a mixture of an angiotensin receptor antagonist and a NEPi; and

(d) isolating the linked pro-drug.

In a fourth aspect, this invention is directed to a method of treating or preventing a disease or condition, such as hypertension, heart failure (acute and chronic), congestive heart failure, left ventricular dysfunction and hypertrophic cardiomyopathy, diabetic cardiac myopathy, supraventricular and ventricular arrhythmias, atrial fibrillation, atrial flutter, detrimental vascular remodeling, myocardial infarction and its sequelae, atherosclerosis, angina (unstable or stable), renal insufficiency (diabetic and non-diabetic), heart failure, angina pectoris, diabetes, secondary aldosteronism, primary and secondary pulmonary hypertension, renal failure conditions, such as diabetic nephropathy, glomerulonephritis, scleroderma, glomerular sclerosis, proteinuria of primary renal disease, and also renal vascular hypertension, diabetic retinopathy, other vascular disorders, such as migraine, peripheral vascular disease, Raynaud's disease, luminal hyperplasia,

cognitive dysfunction (such as Alzheimer's), glaucoma and stroke comprising administering the afore-mentioned dual-acting compound or combination, in particular the supramolecular complex, or the afore-mentioned linked pro-drug, preferably, the complex, to a subject in need of such treatment.

FIG. **1** shows a pictorial representation of the unit cell of the supramolecular complex of trisodium[3-((1S,3R)-1-biphenyl-4-ylmethyl-3-ethoxycarbonyl-1-butylcarbamoyl) propionate-(S)-3'-methyl-2'-(pentanoyl{2"-(tetrazol-5-ylate)biphenyl-4'-ylmethyl}amino)butyrate] hemipentahydrate comprising two asymmetric units. The following color code is used: grey=carbon atom; blue=nitrogen atom; red=oxygen atom; violet=sodium atom

DETAILED DESCRIPTION

The present invention relates to a dual-acting compound or combination, in particular a supramolecular complex, or linked pro-drug or in particular a supramolecular complex of two active agents with different mechanisms of action, namely an angiotensin receptor antagonist and a neutral endopeptidase inhibitor, which can form a unique molecular entity for the treatment of patients with various cardiovascular and/or renal diseases.

One embodiment of the invention is directed to a physical combination comprising:

(a) a pharmaceutically acceptable salt of an angiotensin receptor antagonist; and

(b) a pharmaceutically acceptable salt of a neutral endopeptidase inhibitor (NEPi); wherein the pharmaceutically acceptable salt of the angiotensin receptor antagonist and the NEPi is the same and is selected from a salt of Na, K or NH_4.

Specifically, it is preferred that the two active agents are combined with each other so as to form a single dual-acting compound, in particular a supramolecular complex. By doing so, a new molecular or supramolecular entity is formed having distinct properties different to the above physical combination.

Thus, the present invention is directed to a dual-acting compound, in particular a supramolecular complex, comprising:

(a) an angiotensin receptor antagonist;

(b) a neutral endopeptidase inhibitor (NEPi); and

(c) a pharmaceutically acceptable cation preferably selected from the group consisting of Na, K and NH_4.

The present invention is also directed to a dual-acting compound, in particular a supramolecular complex, obtainable by:

(i) dissolving an angiotensin receptor antagonist and a neutral endopeptidase inhibitor (NEPi) in a suitable solvent;

(ii) dissolving a basic compound of Cat such as (Cat)OH, $(Cat)_2CO_3$, $(Cat)HCO_3$ in a suitable solvent, wherein Cat is a cation preferably selected from the group consisting of Na, K and NH_4;

(iii) combining the solutions obtained in steps (i) and (ii);

(iv) precipitation of the solid, and drying same to obtain the dual-acting compound; or alternatively obtaining the dual-acting compound by exchanging the solvent(s) employed in steps (i) and (ii) by

(iva) evaporating the resulting solution to dryness;

(va) re-dissolving the solid in a suitable solvent;

(via) precipitation of the solid and drying same to obtain the dual-acting compound.

The present invention is further directed to linked pro-drugs comprising:

(a) an angiotensin receptor antagonist or a pharmaceutically acceptable salt thereof; and

(b) a NEPi or a pharmaceutically acceptable salt thereof,

wherein the angiotensin receptor antagonist or a pharmaceutically acceptable salt thereof and the NEPi or a pharmaceutically acceptable salt thereof are linked by a linking moiety.

The two components are each linked to a linking moiety thereby creating a linked pro-drug. Preferably, the linked pro-drug is substantially pure; as used herein, "substantially pure" refers to at least 90%, more preferably at least 95% and most preferably at least 98% purity.

As one preferred embodiment of the present invention, the linked pro-drug has a structure such that by linking the two components with the linking moiety, a supramolecular complex is formed.

For the purpose of the present invention, the term "dual-acting compound" is intended to describe that these compounds have two different modes of action in one compound, one is the angiotensin receptor blockade resulting from the ARB molecular moiety of the compound and the other is the neutral endopeptidase inhibition resulting from the NEPi molecular moiety of the compound.

For the purpose of the present invention, the term "compound" is intended to describe a chemical substance comprising covalent bonds within the two pharmaceutically active agents, the ARB and the NEPi molecular moieties, and non-covalent interactions between these two pharmaceutically active agents, the ARB and the NEPi molecular moieties. Typically, hydrogen bonding can be observed between the two pharmaceutically active agents, the ARB and the NEPi molecular moieties. Ionic bonds can be present between the cation and one or both of the two pharmaceutically active agents, the ARB and the NEPi molecular moieties. Other types of bonds may also be present within the compound such as van der Waals forces. For illustrative purposes, the dual-acting compound of the present invention could be represented as follows:

$$(ARB)\text{-}(L)_m\text{-}(NEPi)$$

wherein L is a linking moiety, such as a cation or is a noncovalent bond and m is an integer from 1 or more. In other words the ARB and NEPi moiety can be connected via non-covalent bonds such as hydrogen bonding. Alternatively or additionally they may be connected via a linking moiety such as a cation.

In one embodiment, the dual-acting compound may be considered to be a linked pro-drug, whereby the linking moiety, such as the cation, linking the two pharmaceutically active agents, the ARB and the NEPi, forms the pro-drug of these agents which are released once the linked pro-drug is ingested and absorbed.

In a preferred embodiment, the dual-acting compound is a complex, in particular a supramolecular complex.

For the purpose of the present invention, the term "supramolecular complex" is intended to describe an interaction between the two pharmaceutically active agents, the cations and any other entity present such as a solvent, in particular water, by means of noncovalent, intermolecular bonding between them. This interaction leads to an association of the species present in the supramolecular complex distinguishing this complex over a physical mixture of the species.

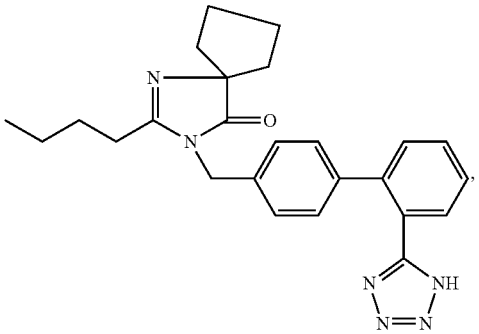
The noncovalent intermolecular bonding can be any interactions known in the art to form such supramolecular complexes, such as hydrogen bonding, van der Waals forces and π-π stacking. Ionic bonds can also be present. Preferably, there exists ionic bonding and additionally hydrogen bonding to form a network of interactions within the complex. The supramolecular complex exists preferably in the solid state but may also be present in liquid media. As a preferred

embodiment of the invention, the complex is crystalline and in this case is preferably a mixed crystal or co-crystal.

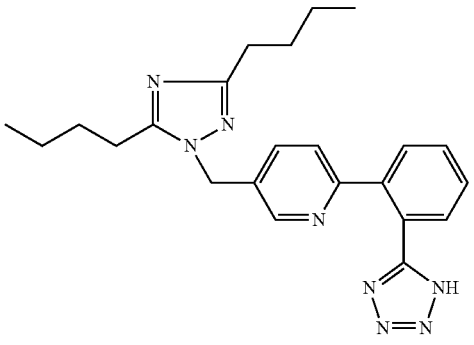
Typically, the dual-acting compound, in particular the supramolecular complex shows properties such as melting point, IR spectrum etc. that are different from a physical mixture of the species.

Preferably, the dual-acting compound, in particular the supramolecular complex, has a network of non-covalent bonds, in particular hydrogen bonds, between the two pharmaceutically active agents and any solvent, if present, preferably water. Moreover, it is preferred that the dual-acting compound, in particular the supramolecular complex, has a network of non-covalent bonds, in particular ionic and hydrogen bonds, between the two pharmaceutically active agents, the cation and any solvent, if present, preferably water. The cation is preferably coordinated to several oxygen ligands, thus, providing a linkage between these oxygen ligands. The oxygen ligands come from the carbonyl and carboxylate groups present in the two pharmaceutically active agents and preferably also from any solvent, if present, preferably water.

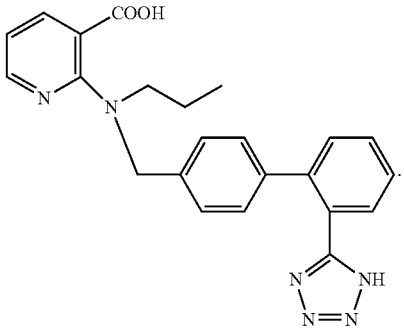
The dual acting compound comprises a molecular moiety of an angiotensin receptor antagonist. This means that a molecular moiety derived from an angiotensin receptor antagonist is participating in the build-up of the dual-acting compound. The angiotensin receptor antagonist is part of the compound and connected to the NEP inhibitor directly or indirectly via non-covalent bonds. For sake of convenience, throughout the application, the term "angiotensin receptor antagonist" will be used when describing this part of the compound. Angiotensin receptor antagonists (ARBs) suitable for use in the present invention include, without limitation, valsartan, losartan, irbesartan, telmisartan, eprosartan, candesartan, olmesartan saprisartan, tasosartan, elisartan, the compound with the designation E-1477 of the following formula



the compound with the designation SC-52458 of the following formula



the compound with the designation the compound ZD-8731 of the following formula



Suitable angiotensin II receptor antagonist also includes, but is not limited to, saralasin acetate, candesartan cilexetil, CGP-63170, EMD-66397, KT3-671, LR-B/081, valsartan, A-81282, BIBR-363, BIBS-222, BMS-184698, candesartan, CV-11194, EXP-3174, KW-3433, L-161177, L-162154, LR-B/057, LY-235656, PD-150304, U-96849, U-97018, UP-275-22, WAY-126227, WK-1492.2K, YM-31472, losartan potassium, E-4177, EMD-73495, eprosartan, HN-65021, irbesartan, L-159282, ME-3221, SL-91.0102, Tasosartan, Telmisartan, UP-269-6, YM-358, CGP-49870, GA-0056, L-159689, L-162234, L-162441, L-163007, PD-123177, A-81988, BMS-180560, CGP-38560A, CGP-48369, DA-2079, DE-3489, DuP-167, EXP-063, EXP-6155, EXP-6803, EXP-7711, EXP-9270, FK-739, HR-720, ICI-D6888, ICI-D7155, ICI-D8731, isoteoline, KRI-1177, L-158809, L-158978, L-159874, LR B087, LY-285434, LY-302289, LY-315995, RG-13647, RWJ-38970, RWJ-46458, S-8307, S-8308, saprisartan, saralasin, Sarmesin, WK-1360, X-6803, ZD-6888, ZD-7155, ZD-8731, BIBS39, CI-996, DMP-811, DuP-532, EXP-929, L-163017, LY-301875, XH-148, XR-510, zolasartan and PD-123319.

Also included within the scope of this aspect of the invention are combinations of the above-identified ARBs.

ARBs to be used for preparing the combination or complex in accordance with the present invention can be purchased from commercial sources or can be prepared according to known methods. ARBs may be used for purposes of this invention in their free form, as well as in any suitable salt or ester form.

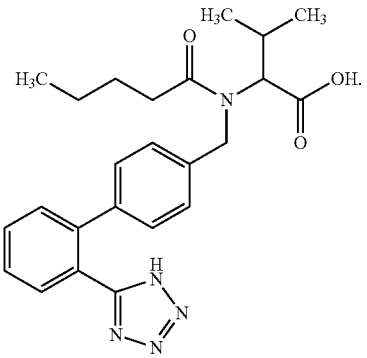
Preferred salts forms include acid addition salts. The compounds having at least one acid group (e.g., COOH or 5-tetrazolyl) can also form salts with bases. Suitable salts with bases are, e.g., metal salts, such as alkali metal or alkaline earth metal salts, e.g., sodium, potassium, calcium or magnesium salts, or salts with ammonia or an organic amine, such as morpholine, thiomorpholine, piperidine, pyrrolidine, a mono-, di- or tri-lower alkylamine, e.g., ethyl-, tert-butyl-, diethyl-, diisopropyl-, triethyl-, tributyl- or dimethylpropylamine, or a mono-, di- or trihydroxy lower alkylamine, e.g., mono-, di- or tri-ethanolamine. Corresponding internal salts may furthermore be formed. Salts which are unsuitable for pharmaceutical uses but which can be employed, e.g., for the isolation or purification of free compounds I or their pharmaceutically acceptable salts, are also included. Even more preferred salts are, e.g., selected from the mono-sodium salt in amorphous form; di-sodium salt of valsartan in amorphous or crystalline form, especially in hydrate form, thereof.

Mono-potassium salt of valsartan in amorphous form; di-potassium salt of valsartan in amorphous or crystalline form, especially in hydrate form, thereof.

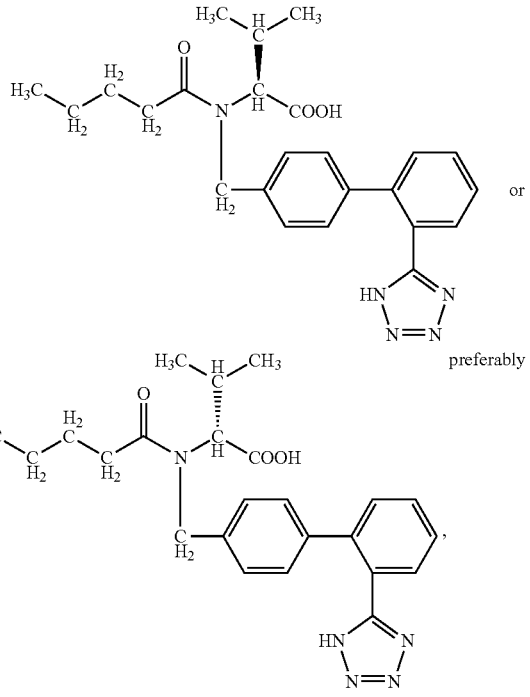
Calcium salt of valsartan in crystalline form, especially in hydrate form, primarily the tetrahydrate thereof; magnesium salt of valsartan in crystalline form, especially in hydrate form, primarily the hexahydrate thereof; calcium/magnesium mixed salt of valsartan in crystalline form, especially in hydrate form; bis-diethylammonium salt of valsartan in crystalline form, especially in hydrate form; bis-dipropylammonium salt of valsartan in crystalline form, especially in hydrate form; bis-dibutylammonium salt of valsartan in crystalline form, especially in hydrate form, primarily the hemihydrate thereof; mono-L-arginine salt of valsartan in amorphous form; bis-L-arginine salt of valsartan in amorphous form; mono-L-lysine salt of valsartan in amorphous form; bis-L-lysine salt of valsartan in amorphous form.

Preferably when preparing the dual-acting compound, in particular the complex according to the present invention, the free form of the ARB is used.

In a preferred embodiment of this invention, the angiotensin receptor blocker used in the combination or complex of the present invention is Valsartan the molecular structure of which is shown below



Valsartan may be in the racemic form or as one of the two isomers shown below



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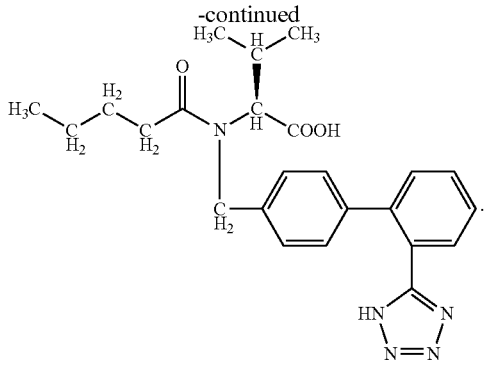


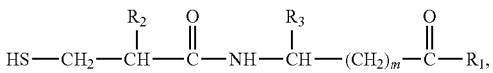
Valsartan ((S)—N-valeryl-N-{[2'-(1H-tetrazole-5-yl)-biphenyl-4-yl]-methyl}-valine) used according to the present invention can be purchased from commercial sources or can be prepared according to known methods. For example, the preparation of valsartan is described in U.S. Pat. No. 5,399,578 and EP 0 443 983, the entire disclosure of each of which is incorporated by reference herein. Valsartan may be used for purposes of this invention in its free acid form, as well as in any suitable salt form. Additionally, esters or other derivatives of the carboxylic grouping may be applied for the synthesis of linked pro-drugs, as well as salts and derivatives of the tetrazole grouping. Reference to ARBs includes reference to pharmaceutically acceptable salts thereof.

Preferably, the ARB is a diprotic acid. Thus, the angiotensin receptor blocker has a charge of 0, 1 or 2 depending on the pH of the solution.

In the combination of the present invention, the ARB is in the form of a pharmaceutically acceptable salt selected from Na, K or NH_4, preferably Na. This includes both the mono- and di-salt of these cations, preferably the di-salt. In particular in the case of valsartan this means that both the carboxylic acid moiety and the tetrazole moiety form the salt.

In the dual-acting compound, in particular the supramolecular complex of the present invention, typically the free form of the ARB is employed in the preparation and the cationic species present in the complex is introduced by using a base, e.g. (Cat)OH.

The dual acting compound comprises a molecular moiety of a neutral endopeptidase inhibitor. This means that a molecular moiety derived from a neutral endopeptidase inhibitor is participating in the build-up of the dual-acting compound. The neutral endopeptidase inhibitor is part of the compound and connected to the ARB directly or indirectly via non-covalent bonds. For sake of convenience, throughout the application, the term "neutral endopeptidase inhibitor" will be used when describing this part of the compound. Neutral endopeptidase inhibitors suitable for use in the present invention include those of formula (I)



(I)

wherein

R_2 is alkyl of 1-7 carbons, trifluoromethyl, phenyl, substituted phenyl, —(CH_2)1 to 4-phenyl, or —(CH_2)1 to 4-substituted phenyl;

R_3 is hydrogen, alkyl of 1-7 carbons, phenyl, substituted phenyl, —(CH_2)1 to 4-phenyl or —(CH_2)1 to 4-substituted phenyl;

R_1 is hydroxy, alkoxy of 1-7 carbons or NH_2;

n is an integer from 1-15;

and the term substituted phenyl refers to a substituent selected from lower alkyl of 1-4 carbons, lower alkoxy of 1-4 carbons, lower alkylthio of 1-4 carbons, hydroxy, Cl, Br or F.

Preferred neutral endopeptidase inhibitors of formula (I) include compounds, wherein

R_2 is benzyl;

R_3 is hydrogen;

n is an integer from 1-9; and

R_1 is hydroxy.

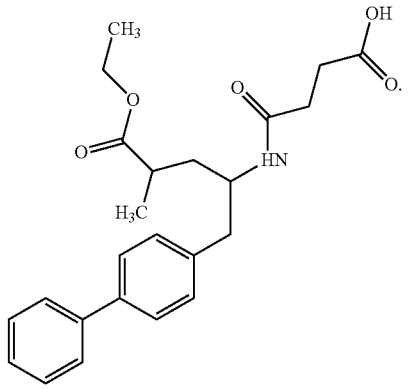
Another preferred neutral endopeptidase inhibitor is (3S, 2'R)-3-{1-[2'-(ethoxycarbonyl)-4'-phenyl-butyl]-cyclopentan-1-carbonylamino}-2,3,4,5-tetrahydro-2-oxo-1H-1-benzazepine-1-acetic acid or a pharmaceutically acceptable salt thereof.

Preferred neutral endopeptidase inhibitors suitable for use in the present invention include, without limitation, SQ 28,603; N—[N-[1 (S)-carboxyl-3-phenylpropyl]-(S)-phenylalanyl]-(S)-isoserine; N—[N-[((1S)-carboxy-2-phenypethyl]-(S)-phenylalanyl]-β-alanine; N-[2(S)-mercaptomethyl-3-(2-methylphenyl)-propionyl]methionine; (cis-4-[[[1-[2-carboxy-3-(2-methoxyethoxy)propyl]-cyclopentyl] carbonyl]amino]-cyclohexanecarboxylic acid); thiorphan; retro-thiorphan; phosphoramidon; SQ 29072; (2R,4S)-5-biphenyl4-yl-5-(3-carboxy-propionylamino)-2-methyl-pentanoic acid ethyl ester; N-(3-carboxy-1-oxopropyl)-(4S)-p-phenylphenylmethyl)-4-amino-2R-methylbutanoic acid; (S)-cis-4-[1-[2-(5-indanyloxycarbonyl)-3-(2-methoxy-ethoxy)propyl]-1-cyclopentanecarboxamido]-1-cyclohexanecarboxylic acid; 3-(1-[6-endo-hydroxymethylbicyclo[2,2,1]heptane-2-exo-carbamoyl]cyclopentyl)-2-(2-methoxyethyl)propanoic acid; N-(1-(3-(N-t-butoxycarbonyl-(S)-prolylamino)-2(S)-t-butoxy-carbonylpropyl)cyclopentanecarbonyl)-O-benzyl-(S)-serine methyl ester; 4-[[2-(mercaptomethyl)-1-oxo-3-phenylpropyl]amino]benzoic acid; 3-[1-(cis-4-carboxycarbonyl-cis-3-butylcyclohexyl-r-1-carbamoyl)cyclopentyl]-2S-(2-methoxyethoxymethyl)propanoic acid; N-((2S)-2-(4-biphenylmethyl)-4-carboxy-5-phenoxyvaleryl)glycine; N-(1-(N-hydroxycarbamoylmethyl)-1-cyclopentanecarbonyl)-L-phenylalanine; (S)-(2-biphenyl-4-yl)-1-(1H-tetrazol-5-yl)ethylamino)methylphosphonic acid; (S)-5-(N-(2-(phosphonomethylamino)-3-(4-biphenyl)propionyl)-2-aminoethyl)tetrazole; β-alanine; 3-[1,1'-biphenyl]-4-yl-N-[diphenoxyphosphinyl)methyl]-L-alanyl; N-(2-carboxy-4-thienyl)-3-mercapto-2-benzylpropanamide; 2-(2-mercaptomethyl-3-phenylpropionamido)thiazol-4-ylcarboxylic acid; (L)-(1-((2,2-dimethyl-1,3-dioxolan-4-yl)-methoxy)carbonyl)-2-phenylethyl)-L-phenylalanyl)-β-alanine; N—[N-[(L)-[1-[(2,2-dimethyl-1,3-dioxolan-4-yl)-methoxy]carbonyl]-2-phenylethyl]-L-phenylalanyl]-(R)-alanine; N—[N-[(L)-1-carboxy-2-phenylethyl]-L-phenylalanyl]-(R)-alanine; N-[2-acetylthiomethyl-3-(2-methyl-phenyl)propionyl]-methionine ethyl ester; N-[2-mercaptomethyl-3-(2-methylphenyl)propionyl]-methionine; N-[2(S)-mercaptomethyl-3-(2-methylphenyl)propanoyl]-(S)-isoserine; N—(S)-[3-mercapto-2-(2-methylphenyl)propionyl]-(S)-2-methoxy-(R)-alanine; N-[1-[[1(S)-benzyloxy-carbonyl-3-phenylpropyl]amino]cyclopentylcarbonyl]-(S)-isoserine; N-[1-[[1(S)-carbonyl-3-phenylpropyl]amino]-cyclopentylcarbonyl]-(S)-isoserine; 1,1'-[dithiobis-[2(S)-(2-methylbenzyl)-1-oxo-3,1-propanediyl]]-bis-(S)-isoserine; 1,1'-[dithiobis-[2(S)-(2-methylbenzyl)-1-oxo-3,1-propanediyl]]-bis-(S)-methionine; N-(3-phenyl-2-(mercaptomethyl)-propionyl)-(S)-4-(methylmercapto)methionine; N-[2-acetylthiomethyl-3-phenyl-propionyl]-3-aminobenzoic acid; N-[2-mercaptomethyl-3-phenyl-propionyl]-3-aminobenzoic acid; N-[1-(2-carboxy-4-phenylbutyl)-cyclopentane-carbonyl]-(S)-isoserine; N-[1-(acetylthiomethyl)cyclopentane-carbonyl]-(S)-methionine ethyl ester; 3(S)-[2-(acetylthiomethyl)-3-phenyl-propionyl]amino-ϵ-caprolactam; N-(2-acetylthiomethyl-3-(2-methylphenyl)propionyl)-methionine ethyl ester; and combinations thereof.

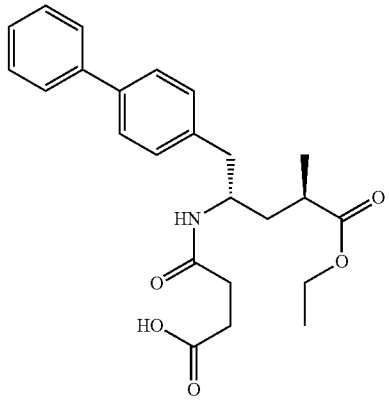
Neutral endopeptidase inhibitors can be purchased from commercial sources or can be prepared according to known methods, such as those set forth in any of U.S. Pat. No. 4,722,810, U.S. Pat. No. 5,223,516, U.S. Pat. No. 4,610,816, U.S. Pat. No. 4,929,641, South African Patent Application 84/0670, UK 69578, U.S. Pat. No. 5,217,996, EP 00342850, GB 02218983, WO 92/14706, EP 00343911, JP 06234754, EP 00361365, WO 90/09374, JP 07157459, WO 94/15908, U.S. Pat. No. 5,273,990, U.S. Pat. No. 5,294,632, U.S. Pat. No. 5,250,522, EP 00636621, WO 93/09101, EP 00590442, WO 93/10773, U.S. Pat. No. 5,217,996, the disclosure of each of which is incorporated by reference. Neutral endopeptidase inhibitors may be used for purposes of this invention in their free form, as well as in any suitable salt form. Reference to neutral endopeptidase inhibitors includes reference to pharmaceutically acceptable salts thereof.

Additionally esters or other derivatives of any carboxylic grouping may be applied for the synthesis of linked prodrugs, as well as salts and derivatives of any other acidic grouping. In a preferred embodiment of this invention, the NEPi is 5-biphenyl4-yl-5-(3-carboxy-propionylamino)-2-methyl-pentanoic acid ethyl ester of formula (II) or the respective hydrolysed form 5-biphenyl4-yl-5-(3-carboxy-propionylamino)-2-methyl-pentanoic acid.

(II)



The compound of formula (II) can exist as the (2R,4S), (2R,4S), (2R,4S) or (2R,4S) isomer. Preferred is (2R,4S)-5-biphenyl4-yl-5-(3-carboxy-propionylamino)-2-methyl-pentanoic acid ethyl ester as shown below:



The compound of formula (II) is a specific inhibitor of NEP and is described in U.S. Pat. No. 5,217,996. It can be purchased from commercial sources or can be prepared according to known methods. The compound of formula (II) may be used for purposes of this invention in its free form, as well as in any suitable salt or ester form.

Preferably the NEPi is a monoprotic acid. Thus, the NEPi has a charge of 0 or 1 depending on the pH of the solution.

In the combination of the present invention, the NEPi is in the form of a pharmaceutically acceptable salt selected from Na, K or NH_4, preferably Na.

In the dual-acting compound, in particular the supramolecular complex of the present invention, typically the free form of the NEPi is employed in the preparation and the cationic species present in the complex is introduced by using a base, (Cat)OH.

The dual acting compound preferably comprises non-covalent bonds between the ARB and the NEPi. Alternatively or in addition, it optionally comprises a linking moiety such as a pharmaceutically acceptable cation.

The linking moiety includes, but is not limited to, generally regarded as safe (GRAS) compounds or other pharmacologically acceptable compounds. The linking moiety may be an ion or a neutral molecule. In the case wherein the linking moiety is an ion the linked pro-drug is a salt and when the linking moiety is a neutral molecule the linked pro-drug is a co-crystal. Without being bound by any particular theory, the acidic portion of the ARB and NEPi donate a proton to the basic linking moiety such that all three components then become united to form one molecule. When the linked pro-drug is ingested by the subject intended to be treated the more acidic nature of the ingestion environment causes the linked pro-drug to separate into individual components concomitant with ingestion and absorption and therefore be converted into active agents to provide their beneficial biological action to treat the intended diseases.

In the case of a linked pro-drug salt or the dual-acting compound, the linking moiety or the cation, respectively, is preferably a positively charged mono-, di- or tri-valent cation, an organic base or an amino acid. Preferred cations (Cat) both for the linked pro-drug in general and the dual-acting compound, in particular the complex are basic cations, even more preferably metallic cations. Preferred metallic cations include, but are not limited to Na, K, Ca, Mg, Zn, Fe or NH_4. Amine bases and salt forming agents may also be employed, such as benzathine, hydrabamine, ethylenediamine, n-n-dibenzyl-ethylenediamine, L-arginine, choline hydroxide, N-methyl-glucamine, (Meglumine), L-Lysine, dimethylaminoethanol (Deanol), t-butylamine, diethylamine, 2-(diethylamino)-ethanol, 4-(2-hydroxyethylmorpholine, Thromethanine (TRIS), 4-acetamidophenol, 2-amino-2-methyl-1,3-propanediol, 2-amino-2-methyl-propanol, benzylamine, cyclohexylamine, diethanolamine, ethanolamine, imidazole, piperazine and triethanolamine.

Most preferably, the cation is Na, K or NH_4, such as Na. In one embodiment Ca is preferred.

In the case of a linked pro-drug co-crystal, the linking moiety is may also be a neutral molecule which provides hydrogen-bonding functionality.

In one embodiment, the linked pro-drugs of this invention are represented as set forth below, wherein scheme (1) and (2) represent a salt and scheme (3) represents a co-crystal:

NEPi.Xa.ARB scheme (1)

NEPi.XaYb.ARB scheme (2)

NEPi.Zc.ARB scheme (3),

wherein

X is Ca, Mg, Zn or Fe;

Y is Na, K or NH4;

Z is a neutral molecule; and

a, b and c reflect the stoichiometry of the linked pro-drug, preferably, a, b and c are a valence of 1^+, 2^+ or 3^+.

For the linked pro-drugs of schemes (1) and (2), above, preferably the NEPi is a monoprotic acid and ARB is a diprotic acid. The angiotensin receptor blocker has a charge of 0, 1 or 2 and the NEPi has a charge of 0 or 1 depending on the pH of the solution, while the overall molecule will be neutral. Ratios of ARB to NEPi will be 1:1, 1:2, 1:3, 3:1, 2:1, 1:1, preferably 1:1, 1:2 or 1:3, most preferably 1:1.

Multi-component salts, particularly with zinc and calcium have been reported in the literature, e.g., *Chem Pharm Bull*, Vol. 53, p. 654 (2005). These ions require a coordination geometry that facilitates the crystallization of multi-component systems. The metal ions have coordinating geometries governed by the atomic orbitals for each species.

Valsartan comprises two acidic groupings: the carboxylic acid and the tetrazole. In one embodiment of this aspect of the present invention, the molecular structure of linked pro-drugs of valsartan and a NEPi comprise a linkage between the carboxylic acid and the linking moiety or a linkage between the tetrazole grouping and the linking moiety. In yet another embodiment, the linked pro-drug comprises a trivalent linking moiety linked to the valsartan carboxylic acid grouping, the tetrazole grouping and the NEPi grouping.

In an embodiment of this aspect of the invention, valsartan is linked to (2R,4S)-5-biphenyl4-yl-5-(3-carboxy-propionylamino)-2-methyl-pentanoic acid ethyl ester by a calcium salt ion.

In a preferred embodiment of the present application, the angiotensin receptor antagonist and the neutral endopeptidase inhibitor are present in a molar ratio of 1:1, 1:2, 1:3, 3:1, 2:1, more preferably 1:1 in the combination as well as in the supramolecular complex. This is also true for the linked pro-drug. Moreover, in the complex, angiotensin receptor antagonist, the neutral endopeptidase inhibitor and the cation are present in a molar ratio of 1:1:1, 1:1:2, 1:1:3, more preferably 1:1:3. This applies equally to the linked pro-drug.

The combination or the dual-acting compound, in particular the complex of the present invention may contain a solvent. This is particularly preferred in the case of the dual-acting compound, in particular the complex, where the solvent may contribute to the intermolecular structure, e.g. the supramolecular interactions. Preferred solvents include water, methanol, ethanol, 2-propanol, acetone, ethyl acetate, methyl-t-butylether, acetonitrile, toluene, and methylene chloride, preferably water. If a solvent is present, one or more molecules per molecule of the active agent can be present. In this case, namely if a stoichiometric amount of the solvent is present, preferably 1, 2, 3, 4 or 5, more preferably 3, molecules of solvent, such as water, can be present per molecule of active agent. Alternatively, the solvent may be present in non-stoichiometric amounts. This means preferably any stoichiometric fraction of the solvent, such as 0.25, 0.5, 0.75, 1.25, 1.5, 1.75, 2.25, 2.5, 2.75, 3.25, 3.5, 3.75, 4.25, 4.5 and 4.75, preferably 2.5, molecules of solvent, such as water, can be present per molecule of active agent. If the dual-acting compound, in particular the complex is in the crystalline form, the solvent may be part of the molecular packing and be trapped in the crystal lattice.

Thus in a preferred embodiment of the present invention, the dual-acting compound, in particular the supramolecular complex is described by the sum formula:

$[ARB(NEPi)]Na_{1-3}.xH_2O$, wherein x is 0, 1, 2 or 3, such as 3, preferably

$[ARB(NEPi)]Na_3.xH_2O$, wherein x is 0, 1, 2 or 3, such as 3, more preferably

[valsartan((2R,4S)-5-biphenyl4-yl-5-(3-carboxy-propionylamino)-2-methyl-pentanoic acid ethyl ester]$Na_3.xH_2O$, wherein x is 0, 1, 2 or 3, such as 3.

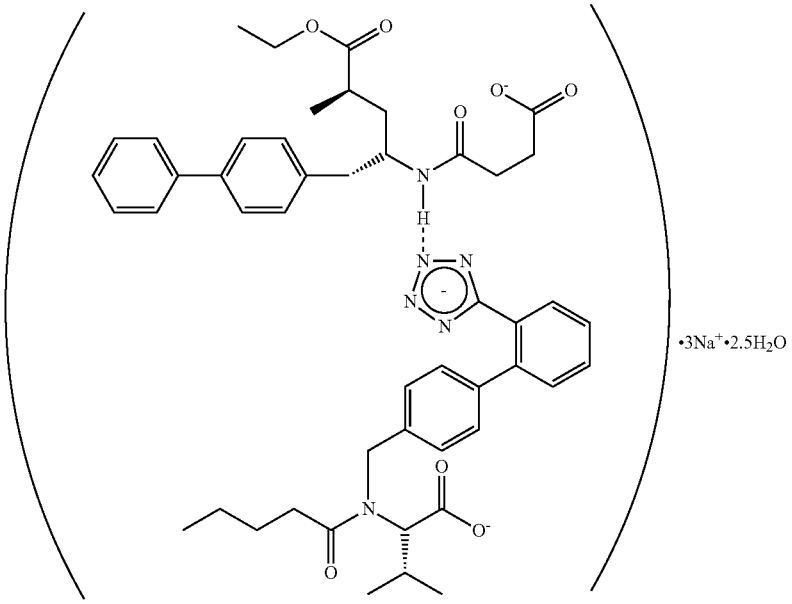
Thus in a preferred embodiment of the present invention, the dual-acting compound, in particular the supramolecular complex is described by the sum formula:

[ARB(NEPi)]$Na_{1-3}.xH_2O$, wherein x is 0 to 3, such as 2.5, preferably

[ARB(NEPi)]$Na_3.xH_2O$, wherein x is 0 to 3, such as 2.5, more preferably

[(N-valeryl-N-{[2'-(1H-tetrazole-5-yl)-biphenyl-4-yl]-methyl}-valine) (5-biphenyl4-yl-5-(3-carboxy-propionylamino)-2-methyl-pentanoic acid ethyl ester]$Na_3.xH_2O$, in particular [((S)—N-valeryl-N-{[2'-(1H-tetrazole-5-yl)-biphenyl-4-yl]-methyl}-valine) ((2R,4S)-5-biphenyl4-yl-5-(3-carboxy-propionylamino)-2-methyl-pentanoic acid ethyl ester]$Na_3.xH_2O$, wherein x is 0 to 3, such as 2.5. In this most preferred example, the complex is termed trisodium[3-((1S,3R)-1-biphenyl-4-ylmethyl-3-ethoxycarbonyl-1-butylcarbamoyl)propionate-(S)-3'-methyl-2'-(pentanoyl{2"-(tetrazol-5-ylate)biphenyl-4'-ylmethyl}amino)butyrate] hemipentahydrate.

A simplified structure of trisodium[3-((1S,3R)-1-biphenyl-4-ylmethyl-3-ethoxycarbonyl-1-butylcarbamoyl)propionate-(S)-3'-methyl-2'-(pentanoyl{2"-(tetrazol-5-ylate)biphenyl-4'-ylmethyl}amino)butyrate]hemipentahydrate used to formally calculate the relative molecular mass, is shown below.



Valsartan comprises two acidic groupings: the carboxylic acid and the tetrazole. In one embodiment of this aspect of the present invention, the molecular structure of the dual-acting compound, in particular, the complex, of valsartan and a NEPi comprises an interaction between the carboxylic acid and the cation, such as Na, or the solvent, such as water, or a linkage between the tetrazole grouping and the cation, such as Na, or the solvent, such as water. In yet another embodiment, the dual-acting compound, in particular, the complex, comprises an interaction between the valsartan carboxylic acid grouping, the tetrazole grouping or the NEPi grouping and the cation, such as Na, or the solvent, such as water.

The combination or dual-acting compound, in particular, the complex, of the present invention is preferably in the solid form. In the solid state it can be in the crystalline, partially crystalline, amorphous, or polymorphous form, preferably in the crystalline form.

The dual-acting compound, in particular, the complex, of the present invention is distinct from a combination of an ARB and a NEPi obtained by simply physically mixing the two active agents. Thus, it can have different properties that make it particularly useful for manufacturing and therapeutic applications. The difference of the dual-acting compound, in particular, the complex, and the combination can be exemplified by the dual-acting compound of (S)—N-valeryl-N-{[2'-(1H-tetrazole-5-yl)-biphenyl-4-yl]-methyl}-valine and (2R,4S)-5-biphenyl4-yl-5-(3-carboxy-propionylamino)-2-methyl-pentanoic acid ethyl ester which is characterized by very distinct spectral peaks and shifts that are not observed in the physical mixture.

Specifically, such a dual-acting compound is preferably characterized by an X-ray powder diffraction pattern taken with a Scintag XDS2000 powder diffractometer using Cu—Ka radiation (lamda=1.54056 A) with a Peltier-cooled Silicon detector at room temperature (25 degree C.). Scan range was from 1.5 degree to 40 degree in 2 theta with a scan rate of 3 degree/minute. The most important reflections in the X-ray diffraction diagram comprise the following interlattice plane intervals:

The preferred characterization of trisodium[3-((1S,3R)-1-biphenyl-4-ylmethyl-3-ethoxycarbonyl-1-butylcarbamoyl) propionate-(S)-3'-methyl-2'-(pentanoyl{2"-(tetrazol-5-ylate)biphenyl-4'-ylmethyl}amino)butyrate] hemipentahydrate is obtained from the interlattice plane intervals d of the ascertained X-ray diffraction diagrams, whereby, in the following, average values 2θ in [°] are indicated (error limit of ±0.2)

4.5, 5.5, 5.6, 9.9, 12.8, 15.7, 17.0, 17.1, 17.2, 18.3, 18.5, 19.8, 21.5, 21.7, 23.2, 23.3, 24.9, 25.3, 27.4, 27.9, 28.0, 30.2.

or with an error limit of ±0.1:

4.45, 5.52, 5.57, 9.94, 12.82, 15.66, 17.01, 17.12, 17.2, 18.32, 18.46, 19.76, 21.53, 21.72, 23.17, 23.27, 24.88, 25.3, 27.4, 27.88, 28.04, 30.2.

The most intensive reflections in the X-ray diffraction pattern show the following interlattice plane intervals:

2θ in [°]: 4.5, 5.6, 12.8, 17.0, 17.2, 19.8, 21.5, 27.4, in particular 4.45, 5.57, 17.01, 17.2, 19.76, 21, 27.4.

A preferred method of checking the above-indicated average values of the interlattice plane intervals and intensities measured by experimentation from X-ray diffraction, for a given substance, consists in calculating these intervals and their intensities from the comprehensive single crystal structure determination. This structure determination yields cell constants and atom positions, which enable the X-ray diffraction diagram corresponding to the solid to be calculated by means of computer-aided calculation methods. The program used is Powder Pattern within the application software Materials Studio (Accelrys). A comparison of these data, namely the interlattice plane intervals and intensities of the most important lines of trisodium[3-((1S,3R)-1-biphenyl-4-ylmethyl-3-ethoxycarbonyl-1-butylcarbamoyl)propionate-(S)-3'-methyl-2'-(pentanoyl{2"-(tetrazol-5-ylate)biphenyl-4'-ylmethyl}amino)butyrate]hemipentahydrate, obtained from measurements and from calculating the single crystal data, is illustrated in the table below.

TABLE

measured		calculated		measured		calculated	
2θ in [°]	Intensity	2θ in [°]	Intensity	2θ in [°]	Intensity	2θ in [°]	Intensity
4.45	very strong	4.15	very strong	19.76	strong	19.6	very weak
5.52	Strong	5	strong	21.53	weak	19.8	very weak
5.57	strong	6.5	strong	21.72	very weak	21.4	very weak
9.94	very weak	9.75	weak	23.17	weak	23.1	very weak
12.82	very strong	12.6	weak	23.27	weak	23.15	very weak
15.66	very weak	15.05	strong	24.88	very weak		very weak
17.01	weak	16.9	very strong	25.3	weak	25.3	very weak
17.12	strong	17.1	strong	27.4	weak	27.3	very weak
17.2	weak	17.15	weak	27.88	very weak	27.9	very weak
18.32	weak	18.25	very weak	28.04	weak		
18.46	weak	18.3	weak	30.2	weak		

Relative intensity between 100% to 50% is referred to as very strong, 50% to 10% as strong, 10% to 5% as weak, and below 5% as very weak.

The invention relates to trisodium[3-((1S,3R)-1-biphenyl-4-ylmethyl-3-ethoxycarbonyl-1-butylcarbamoyl)propionate-(S)-3'-methyl-2'-(pentanoyl{2"-(tetrazol-5-ylate)biphenyl-4'-ylmethyl}amino)butyrate]hemipentahydrate, a crystalline solid which is characterized by the data and parameters obtained from single crystal X-ray analysis and X-ray powder patterns. An in-depth discussion of the theory of the methods of single crystal X-ray diffraction and the definition of the evaluated crystal data and the parameters may be found in Stout & Jensen, X-Ray Structure Determination; A Practical Guide, Mac Millian Co., New York, N.Y. (1968) chapter 3.

Crystal data	
sum formula	$C_{48}H_{55}N_6O_8Na_3 \cdot 2.5H_2O$
molecular mass	957.99
crystal colour	colourless
crystal shape	tabular: hexagonal
crystal system	monoclinic
space group	$P2_1$
Cell parameters	a = 20.344 Å
	b = 42.018 Å
	c = 20.374 Å
	α = 90°
	β = 119.29°
	γ = 90°
volume of unit cell	15190.03 $Å^3$
Z (the number of asymmetric units in the unit cell)	2
calculated density	1.26845 g/cm3
Single crystal X-ray measurement data	
diffractometer	Nonius KappaCCD
X-ray generator	Nonius FR571 X-ray generator with a copper rotating anode
temperature	270 K and 150 K

Notes:
Two data sets on two suitable single crystals were collected at two different temperatures to assure no phase change during cooling.
None of the hydrogen atoms on the water or amine nitrogen atoms were observed in the Fourier maps so they were not included in the refinement.

Computer Program Used to Solve the Structure
SHELXD (Sheldrick, Göttingen)

In three dimensions, the unit cell is defined by three edge lengths a, b, and c, and three interaxial angles α, β, and γ. In this way, the volume of the unit cell V_c is determined. A differentiated description of these crystal parameters is illustrated in chapter 3 of Stout & Jensen (see above). The details for trisodium[3-((1S,3R)-1-biphenyl-4-ylmethyl-3-ethoxycarbonyl-1-butylcarbamoyl)propionate-(S)-3'-methyl-2'-(pentanoyl{2"-(tetrazol-5-ylate)biphenyl-4'-ylmethyl}amino)butyrate]hemipentahydrate from the single crystal measurements, especially the atom coordinates, the isotropic thermal parameters, the coordinates of the hydrogen atoms as well as the corresponding isotropic thermal parameters, show that a monoclinic unit cell exists, its cell content of twelve formula units of $C_{48}H_{55}N_6O_8Na_3.2.5H_2O$ occurring as a result of two asymmetric units on two-fold positions.

The acentric space group $P2_1$ determined from the single crystal X-ray structure is a common space group for enantiomorphically pure molecules. In this space group there are two general positions which means that for twelve formula units in the unit cell there must be 18 sodium ions and 15 waters in the asymmetric unit.

A pictorial representation of the unit cell of the supramolecular complex of trisodium[3-((1S,3R)-1-biphenyl-4-ylmethyl-3-ethoxycarbonyl-1-butylcarbamoyl)propionate-(S)-

3'-methyl-2'-(pentanoyl{2"-(tetrazol-5-ylate)biphenyl-4'-ylmethyl}amino)butyrate]hemipentahydrate comprising two asymmetric units is shown in FIG. **1**.

Based on the single crystal structure solution, the asymmetric unit of the trisodium[3-((1S,3R)-1-biphenyl-4-ylmethyl-3-ethoxycarbonyl-1-butylcarbamoyl)propionate-(S)-3'-methyl-2'-(pentanoyl{2"-(tetrazol-5-ylate)biphenyl-4'-ylmethyl}amino)butyrate]hemipentahydrate supramolecule comprises six each of ARB and NEPi moieties, 18 sodium atoms, and 15 water molecules. Trisodium[3-((1S,3R)-1-biphenyl-4-ylmethyl-3-ethoxycarbonyl-1-butylcarbamoyl) propionate-(S)-3'-methyl-2'-(pentanoyl{2"-(tetrazol-5-ylate)biphenyl-4'-ylmethyl}amino)butyrate] hemipentahydrate may be considered a sodium supramolecular complex, coordinated by oxygen ligands. These oxygens come from twelve carboxylate groups and eighteen carbonyl groups of the above moieties, and from 13 of the 15 water molecules. The crystal is an infinite 3-dimensional network of these sodium complexes.

Such a compound may also be characterized by an infrared absorption spectrum obtained using Attenuated Total Reflection Fourier Transform Infrared (ATR-FTIR) spectrometer (Nicolet Magna-IR 560) showing the following significant bands, expressed in reciprocal wave numbers (cm^{-1}):

2956 (w), 1711 (st), 1637 (st), 1597 (st), 1488 (w), 1459 (m), 1401 (st), 1357 (w), 1295 (m), 1266 (m), 1176 (w), 1085 (m), 1010 (w), 1942(w), 907 (w), 862 (w), 763 (st), 742 (m), 698 (m), 533 (st). Characteristic to the complex are in particular the following peaks 1711(st), 1637(st), 1597(st) and 1401(st). The error margin for all absorption bands of ATR-IR is ±2 cm^{-1}. The intensities of the absorption bands are indicated as follows: (w)=weak; (m)=medium; and (st)=strong intensity.

Such a compound may also be characterized by a Raman spectrum measured by dispersive Raman spectrometer with 785 nm laser excitation source (Kaiser Optical Systems, Inc.) showing the following significant bands expressed in reciprocal wave numbers (cm^{-1}):

3061 (m), 2930 (m, broad), 1612 (st), 1523 (m), 1461 (w), 1427 (w), 1287 (st), 1195 (w), 1108 (w), 11053 (w), 1041 (w), 1011 (w), 997 (m), 866(w), 850 (w), 822 (w), 808 (w), 735 (w), 715 (w), 669 (w), 643 (w), 631 (w), 618 (w), 602 (w), 557 (w), 522 (w), 453 (w), 410 (w), 328 (w).

The error margin for all Raman bands is ±2 cm^{-1}. The intensities of the absorption bands are indicated as follows: (w)=weak; (m)=medium; and (st)=strong intensity.

Such a compound may also be characterized by distinct melting properties measured by differential scanning calorimetry (DSC). Using Q1000 (TA Instruments) instrument, the melting onset temperature and the peak maximum temperature for such a complex are observed at 139° C. and 145° C., respectively. The heating rate is 10 K/min.

The second embodiment of the present invention is directed to pharmaceutical compositions comprising a combination, a linked pro-drug or a dual-acting compound, in particular the complex as described herein and at least one pharmaceutically acceptable additive. The details regarding the combination and the complex, including the ARB and the NEPi, are as described above with regard to the first embodiment of the invention.

The pharmaceutical compositions according to the invention can be prepared in a manner known per se and are those suitable for enteral, such as oral or rectal, and parenteral administration to mammals (warm-blooded animals), including man, comprising a therapeutically effective amount of the combination or dual-acting compound, in particular the complex, alone or in combination with at least one pharmaceutically acceptable carrier, especially suitable for enteral or parenteral application. Typical oral formulations include tablets, capsules, syrups, elixirs and suspensions. Typical injectable formulations include solutions and suspensions.

Pharmaceutically acceptable additives suitable for use in the present invention include, without limitation and provided they are chemically inert so that they do not adversely affect the combination or the dual-acting compound, in particular the complex of the present invention, diluents or fillers, disintegrants, glidants, lubricants, binders, colorants and combinations thereof. The amount of each additive in a solid dosage formulation may vary within ranges conventional in the art. Typical pharmaceutically acceptable carriers for use in the formulations described above are exemplified by: sugars, such as lactose, sucrose, mannitol and sorbitol; starches, such as cornstarch, tapioca starch and potato starch; cellulose and derivatives, such as sodium carboxymethyl cellulose, ethyl cellulose and methyl cellulose; calcium phosphates, such as dicalcium phosphate and tricalcium phosphate; sodium sulfate; calcium sulfate; polyvinylpyrrolidone; polyvinyl alcohol; stearic acid; alkaline earth metal stearates, such as magnesium stearate and calcium stearate; stearic acid; vegetable oils, such as peanut oil, cottonseed oil, sesame oil, olive oil and corn oil; non-ionic, cationic and anionic surfactants; ethylene glycol polymers; β-cyclodextrin; fatty alcohols; and hydrolyzed cereal solids, as well as other non-toxic compatible fillers, binders, disintegrants, buffers, preservatives, antioxidants, lubricants, flavoring agents and the like commonly used in pharmaceutical formulations.

Pharmaceutical preparations for enteral or parenteral administration are, e.g., in unit dose forms, such as coated tablets, tablets, capsules or suppositories and also ampoules. These are prepared in a manner which is known per se, e.g., using conventional mixing, granulation, coating, solubilizing or lyophilizing processes. Thus, pharmaceutical compositions for oral use can be obtained by combining the linked pro-drug, combination or dual-acting compound, in particular the complex with solid excipients, if desired, granulating a mixture which has been obtained, and, if required or necessary, processing the mixture or granulate into tablets or coated tablet cores after having added suitable auxiliary substances.

The dosage of the active compounds in the combination or dual-acting compound, in particular the complex can depend on a variety of factors, such as mode of administration, homeothermic species, age and/or individual condition. The projected efficacy in animal disease models ranges from about 0.1 mg/kg/day to about 1000 mg/kg/day given orally, and the projected dose for human treatment ranges from about 0.1 mg/day to about 2000 mg/day. Preferred ranges are from about 40 mg/day to about 960 mg/day of the linked pro-drug, preferably about 80 mg/day to about 640 mg/day. The ARB component is administered in a dosage of from about 40 mg/day to about 320 mg/day and the NEPi component is administered in a dosage of from about 40 mg/day to about 320 mg/day. More specifically, the dosages of ARB/NEPi, respectively, include 40 mg/40 mg, 80 mg/80 mg, 160 mg/160 mg, 320 mg/320 mg, 40 mg/80 mg, 80 mg/160 mg, 160 mg/320 mg, 320 mg/640 mg, 80 mg/40 mg, 160 mg/80 mg and 320 mg/160 mg, respectively. These dosages are "therapeutically effective amounts". Preferred dosages for the linked pro-drug, combination or dual-acting compound, in particular the complex of the pharmaceutical composition according to the present invention are therapeutically effective dosages.

The pharmaceutical compositions may contain in addition another therapeutic agent, e.g., each at an effective therapeutic dose as reported in the art. Such therapeutic agents include:

a) antidiabetic agents such as insulin, insulin derivatives and mimetics; insulin secretagogues such as the sulfonylureas, e.g., Glipizide, glyburide and Amaryl; insulinotropic sulfonylurea receptor ligands such as meglitinides, e.g., nateglinide and repaglinide; peroxisome proliferator-activated receptor (PPAR) ligands; protein tyrosine phosphatase-1B (PTP-1B) inhibitors such as PTP-112; GSK3 (glycogen synthase kinase-3) inhibitors such as SB-517955, SB-4195052, SB-216763, NN-57-05441 and NN-57-05445; RXR ligands such as GW-0791 and AGN-194204; sodium-dependent glucose cotransporter inhibitors such as T-1095; glycogen phosphorylase A inhibitors such as BAY R3401; biguanides such as metformin; alpha-glucosidase inhibitors such as acarbose; GLP-1 (glucagon like peptide-1), GLP-1 analogs such as Exendin-4 and GLP-1 mimetics; and DPPIV (dipeptidyl peptidase IV) inhibitors such as LAF237;

b) hypolipidemic agents such as 3-hydroxy-3-methyl-glutaryl coenzyme A (HMG-CoA) reductase inhibitors, e.g., lovastatin, pitavastatin, simvastatin, pravastatin, cerivastatin, mevastatin, velostatin, fluvastatin, dalvastatin, atorvastatin, rosuvastatin and rivastatin; squalene synthase inhibitors; FXR (farnesoid X receptor) and LXR (liver X receptor) ligands; cholestyramine; fibrates; nicotinic acid and aspirin;

c) anti-obesity agents such as orlistat; and

d) anti-hypertensive agents, e.g., loop diuretics such as ethacrynic acid, furosemide and torsemide; angiotensin converting enzyme (ACE) inhibitors such as benazepril, captopril, enalapril, fosinopril, lisinopril, moexipril, perinodopril, quinapril, ramipril and trandolapril; inhibitors of the Na-K-ATPase membrane pump such as digoxin; ACE/NEP inhibitors such as omapatrilat, sampatrilat and fasidotril; β-adrenergic receptor blockers such as acebutolol, atenolol, betaxolol, bisoprolol, metoprolol, nadolol, propranolol, sotalol and timolol; inotropic agents such as digoxin, dobutamine and milrinone; calcium channel blockers such as amlodipine, bepridil, diltiazem, felodipine, nicardipine, nimodipine, nifedipine, nisoldipine and verapamil; aldosterone receptor antagonists; and aldosterone synthase inhibitors. Most preferred combination partners are diuretics, such as hydrochlorothiazide, and/or calcium channel blockers, such as amlodipine or a salt thereof.

Other specific anti-diabetic compounds are described by Patel Mona in *Expert Opin Investig Drugs,* 2003, 12(4), 623-633, in the FIGS. 1 to 7, which are herein incorporated by reference. A compound of the present invention may be administered either simultaneously, before or after the other active ingredient, either separately by the same or different route of administration or together in the same pharmaceutical formulation.

The structure of the therapeutic agents identified by code numbers, generic or trade names may be taken from the actual edition of the standard compendium "The Merck Index" or from databases, e.g., Patents International (e.g. IMS World Publications). The corresponding content thereof is hereby incorporated by reference.

Accordingly, the present invention provides pharmaceutical compositions in addition a therapeutically effective amount of another therapeutic agent, preferably selected from antidiabetics, hypolipidemic agents, anti-obesity agents or anti-hypertensive agents, most preferably from antidiabetics, anti-hypertensive agents or hypolipidemic agents as described above.

The person skilled in the pertinent art is fully enabled to select a relevant test model to prove the efficacy of a combination of the present invention in the hereinbefore and hereinafter indicated therapeutic indications.

Representative studies are carried out with trisodium[3-((1S,3R)-1-biphenyl-4-ylmethyl-3-ethoxycarbonyl-1-butylcarbamoyl)propionate-(S)-3'-methyl-2'-(pentanoyl{2"-(tetrazol-5-ylate)biphenyl-4'-ylmethyl}amino)butyrate] hemipentahydrate, e.g. applying the following methodology:

The antihypertensive and neutral endopeptidase 24.11 (NEP)-inhibitory activities of trisodium[3-((1S,3R)-1-biphenyl-4-ylmethyl-3-ethoxycarbonyl-1-butylcarbamoyl)propionate-(S)-3'-methyl-2'-(pentanoyl{2"-(tetrazol-5-ylate)biphenyl-4'-ylmethyl}amino)butyrate]hemipentahydrate is assessed in conscious rats. The blood pressure-lowering effect is evaluated in double-transgenic rats (dTGRs) that overexpress both human renin and its substrate, human angiotensinogen (Bohlender, et al, High human renin hypertension in transgenic rats. Hypertension; 29(1 Pt 2):428-34, 1997). Consequently, these animals exhibit an angiotensin II-dependent hypertension. The NEP-inhibitory effect of trisodium[3-((1S,3R)-1-biphenyl-4-ylmethyl-3-ethoxycarbonyl-1-butylcarbamoyl)propionate-(S)-3'-methyl-2'-(pentanoyl{2"-(tetrazol-5-ylate)biphenyl-4'-ylmethyl}amino)butyrate] hemipentahydrate is determined in conscious Sprague-Dawley rats infused with exogenous atrial natriuretic peptide (ANP). Potentiation of plasma ANP levels is used as an index of NEP inhibition in vivo. In both models, trisodium[3-((1S,3R)-1-biphenyl-4-ylmethyl-3-ethoxycarbonyl-1-butylcarbamoyl)propionate-(S)-3'-methyl-2'-(pentanoyl{2"-(tetrazol-5-ylate)biphenyl-4'-ylmethyl}amino)butyrate] hemipentahydrate is administered orally as a powder in gelatin mini capsules. The results are summarized below.

- Trisodium[3-((1S,3R)-1-biphenyl-4-ylmethyl-3-ethoxycarbonyl-1-butylcarbamoyl)propionate-(S)-3'-methyl-2'-(pentanoyl{2"-(tetrazol-5-ylate)biphenyl-4'-ylmethyl}amino)butyrate]hemipentahydrate exhibits a dose-dependent and long-lasting antihypertensive effect after oral administration in conscious dTGRs, a rat model of fulminant hypertension.
- Oral administration of trisodium[3-((1S,3R)-1-biphenyl-4-ylmethyl-3-ethoxycarbonyl-1-butylcarbamoyl)propionate-(S)-3'-methyl-2'-(pentanoyl{2"-(tetrazol-5-ylate)biphenyl-4'-ylmethyl}amino)butyrate] hemipentahydrate rapidly and dose-dependently inhibits NEP with a long duration of action, as reflected by its potentiation of plasma ANP immunoreactivity (ANPir) in conscious Sprague-Dawley rats infused with exogenous ANP.

Antihypertensive Effect In Vivo

The dTGRs are instrumented with radiotelemetry transmitters for continuous measurement of arterial blood pressure and heart rate. Animals are randomly assigned to vehicle (empty capsule) or treatment (at 2, 6, 20 or 60 mg/kg, p.o.) groups. Baseline 24-hr mean arterial pressure (MAP) is approximately 170-180 mmHg in all groups. Trisodium[3-((1S,3R)-1-biphenyl-4-ylmethyl-3-ethoxycarbonyl-1-butylcarbamoyl)propionate-(S)-3'-methyl-2'-(pentanoyl{2"-(tetrazol-5-ylate)biphenyl-4'-ylmethyl}amino)butyrate] hemipentahydrate dose-dependently reduces MAP. The values obtained from the treatment groups are dose-dependent, and the results from the three highest doses are significantly different from the vehicle controls

Inhibition of NEP In Vivo

The extent and duration of trisodium[3-((1S,3R)-1-biphenyl-4-ylmethyl-3-ethoxycarbonyl-1-butylcarbamoyl)propionate-(S)-3'-methyl-2'-(pentanoyl{2"-(tetrazol-5-ylate)bi-

phenyl-4'-ylmethyl}amino)butyrate]hemipentahydrate for NEP inhibition in vivo is assessed with methodologies as described previously (Trapani, et al, CGS 35601 and its orally active prodrug CGS 37808 as triple inhibitors of endothelin-converting enzyme-1, neutral endopeptidase 24.11, and angiotensin-converting enzyme. J Cardiovasc Pharmacol; 44(Suppl 1):S211-5, 2004). Rat ANP(1-28) is infused intravenously at a rate of 450 ng/kg/min in conscious, chronically cannulated, male Sprague-Dawley rats. After one hour of infusion, rats are randomly assigned to one of six groups: untreated control, vehicle (empty capsule) control, or one of four doses of drug (2, 6, 20, or 60 mg/kg, p.o.). ANP infusion is continued for an additional eight hours. Blood samples are collected for measuring plasma ANPir by a commercial enzyme immunoassay kit at −60 min (i.e., before initiating ANP infusion), −30 min (after 30 min of ANP infusion), 0 min ("baseline"; after 60 min of ANP infusion but before dosing with drug or its vehicle), and at 0.25, 0.5, 1, 2, 3, 4, 5, 6, 7, and 8 hr post-dosing.

Before ANP infusion, ANPir is low (0.9-1.4 ng/ml) and similar in all six groups. ANP infusion rapidly (by 30 min) elevates ANPir to ~10 ng/ml. This ANPir level is sustained for the duration of the experiment in the untreated and vehicle control groups. In contrast, trisodium[3-((1S,3R)-1-biphenyl-4-ylmethyl-3-ethoxycarbonyl-1-butylcarbamoyl)propionate-(S)-3'-methyl-2'-(pentanoyl{2"-(tetrazol-5-ylate)biphenyl-4'-ylmethyl}amino)butyrate]hemipentahydrate rapidly (within 15 min) and dose-dependently augments ANPir. In summary, orally administered LCZ696 rapidly and dose-dependently inhibited NEP with a long duration of action as reflected by the potentiation of plasma ANPir.

The available results indicate an unexpected therapeutic effect of a compound according to the invention.

In a third aspect, the present invention is directed to a method of making a linked pro-drug of an ARB or a pharmaceutically acceptable salt thereof and a NEPi or a pharmaceutically acceptable salt thereof comprising the steps of:

(a) adding an inorganic salt forming agent to a solvent to form a linked pro-drug salt forming solution;

(b) adding the salt forming solution to a mixture of an ARB and a NEPi such that the ARB and NEPi form a linked pro-drug; and

(c) isolating the linked pro-drug.

Preferably, the components are added in an equivalent amount.

The inorganic salt forming agent includes, but is not limited to, calcium hydroxide, zinc hydroxide, calcium methoxide, calcium acetate, calcium hydrogen carbonate, calcium formate, magnesium hydroxide, magnesium acetate, magnesium formate and magnesium hydrogen carbonate, sodium hydroxide, sodium methoxide, sodium acetate, sodium formate. The inorganic salt forming agent releases the linking moiety into the solvent such that when an ARB and a NEPi are present a linked pro-drug is formed.

Solvents included in the scope of the present invention include, but are not limited to, solvents in which the ARB, NEPi and inorganic salt forming agent preferably exhibit a lower solubility that allows the linked pro-drug to crystallize. Such solvents may comprise, but are not limited to, water, methanol, ethanol, 2-propanol, ethylacetate, methyl-t-butylether, acetonitrile, toluene, and methylene chloride and mixtures of such solvents.

The inorganic salt forming agent and the solvent when combined should have a pH which promotes linked pro-drug formation. The pH may be between about 2 and about 6, preferably between about 3 and about 5, most preferably between 3.9 and 4.7.

The linked pro-drug is isolated by crystallization and chromatography. Specific types of chromatography include, e.g., ligand specific resin chromatography, reverse phase resin chromatography and ion-exchange resin chromatography.

A specific example comprises contacting a divalent salt of one component with a monovalent salt of the other component of the linked pro-drug. Specifically the mixed salt of valsartan and a mono-basic NEPi are synthesized by contacting the calcium salt of valsartan with the sodium salt of the NEPi component. Isolation of the desired mixed salt is carried out by selective crystallization or chromatography using ligand specific resins, reverse phase resins or ion-exchange resins. Similarly this process can be conducted with a monovalent salt of both components, such as the sodium salt of both components.

In another embodiment of this aspect of the invention, a co-crystal of the linked pro-drug is obtained. In a method of making a linked pro-drug co-crystal the inorganic salt forming agent is replaced with a neutral molecule which provides hydrogen binding properties. The solvent may be part of the molecular packing and be trapped in the crystal lattice.

In a preferred embodiment of the third aspect, the present invention is directed to a method of preparing a dual-acting compound comprising

(a) an angiotensin receptor antagonist;

(b) a neutral endopeptidase inhibitor (NEPi); and optionally

(c) a pharmaceutically acceptable cation; said method comprising the steps of:

(i) dissolving an angiotensin receptor antagonist and a neutral endopeptidase inhibitor (NEPi) in a suitable solvent;

(ii) dissolving a basic compound of Cat in a suitable solvent, wherein Cat is a cation;

(iii) combining the solutions obtained in steps (i) and (ii);

(iv) precipitation of the solid, and drying same to obtain the dual-acting compound; or alternatively

obtaining the dual-acting compound by exchanging the solvent(s) employed in steps (i) and (ii) by

(iva) evaporating the resulting solution to dryness;

(va) re-dissolving the solid in a suitable solvent;

(via) precipitation of the solid and drying same to obtain the dual-acting compound.

The details regarding the complex, including the ARB, the NEPi and the cation, are as described above with regard to the first embodiment of the invention.

Preferably, in step (i) the ARB and the NEPi are added in an equivalent molar amount. Both the ARB and the NEPi are preferably used in the free form. The solvent used in step (i) may be any solvent that allows dissolution of both the ARB and the NEPi. Preferred solvents include those mentioned above, namely water, methanol, ethanol, 2-propanol, acetone, ethyl acetate, isopropyl acetate, methyl-t-butylether, acetonitrile, toluene, DMF, NMF and methylene chloride and mixtures of such solvents, such as ethanol-water, methanol-water, 2-propanol-water, acetonitrile-water, acetone-water, 2-propanol-toluene, ethyl acetate-heptane, isopropyl acetate-acetone, methyl-t-butyl ether-heptane, methyl-t-butyl ether-ethanol, ethanol-heptane, acetone-ethyl acetate, actetone-cyclohexane, toluene-heptane, more preferably acetone.

Preferably, in step (ii) the basic compound of Cat is a compound capable of forming a salt with the acidic functionalities of the ARB and the NEPi. Examples include those mentioned above, such as calcium hydroxide, zinc hydroxide, calcium methoxide, calcium ethoxide, calcium acetate, calcium hydrogen carbonate, calcium formate, magnesium hydroxide, magnesium acetate, magnesium formate, magne-

sium hydrogen carbonate, sodium hydroxide, sodium carbonate, sodium hydrogen carbonate, sodium methoxide, sodium ethoxide, sodium acetate, sodium formate, potassium hydroxide, potassium carbonate, potassium hydrogen carbonate, potassium methoxide, potassium ethoxide, potassium acetate, potassium formate, ammonium hydroxide, ammonium methoxide, ammonium ethoxide, and ammonium carbonate. Perchlorates may also be used. Amine bases or salt forming agents such a those mentioned above may also be used, in particular benzathine, L-arginine, cholin, ethylene diamine, L-lysine or piperazine. Typically an inorganic base is employed with Cat as specified herein. More preferably, the basic compound is (Cat)OH, $(Cat)_2CO_3$, $(Cat)HCO_3$, still more preferably Cat(OH), such as NaOH. The basic compound is employed in an amount of at least 3 equivalents relative to either the ARB or the NEPi, preferably it is employed in stoichiometric amount to obtain the dual-acting compound, in particular the complex with three cations. The solvent used in step (ii) may be any solvent or mixtures of solvents that allow dissolution of Cat(OH). Preferred solvents include water, methanol, ethanol, 2-propanol, acetone, ethylacetate, isopropyl acetate, methyl-t-butylether, acetonitrile, toluene, and methylene chloride and mixtures of such solvents, more preferably water.

In step (iii) the solutions obtained in steps (i) and (ii) are combined. This can take place by adding the solution obtained in step (i) to the solution obtained in step (ii) or vice versa, preferably, the solution obtained in step (ii) to the solution obtained in step (i).

According to the first alternative, once combined and preferably mixed, the dual-acting compound, in particular the complex precipitates in step (iv). This mixing and precipitation is typically effected by stirring the solutions for an appropriate amount of time such as 20 min to 6 h, preferably 30 min to 3 h, more preferably 2 h, at room temperature. It is advantageous to add seeds of the dual acting compound. This method facilitates precipitation.

In step (iv) according to this first alternative, a co-solvent is typically added. The co-solvent employed is a solvent in which the ARB and the NEPi in the complexed form exhibit a lower solubility that allows the compound to precipitate. Distillation, either continuous or stepwise, with replacement by this co-solvent results in a mixture predominantly of the co-solvent. Preferred solvents include ethanol, 2-propanol, acetone, ethylacetate, isopropyl acetate, methyl-t-butylether, acetonitrile, toluene, and methylene chloride and mixtures of such solvents, more preferably isopropyl acetate. Preferably, a minimum amount of solvent is employed to facilitate precipitation. The solid is collected, e.g. by filtration, and is dried to obtain the dual-acting compound, in particular the complex in accordance with the present invention. The drying step can be performed at room temperature or elevated temperature such as 30 to 60° C., preferably 30 to 40° C. Reduced pressure can be employed to facilitate removal of the solvent, preferably, drying is effected at ambient pressure or reduced pressure of e.g. 10 to 30 bar, such as 20 bar.

According to a second alternative, once combined and preferably mixed, the dual-acting compound, in particular the complex the mixture preferably forms a clear solution. This mixing is typically effected by stirring the solutions for an appropriate amount of time such as 20 min to 6 h, preferably 30 min to 3 h, more preferably 1 h, at room temperature. If necessary, the temperature may be raised so as to ensure a clear solution.

The obtained mixture is then further treated by solvent exchange to obtain the dual-acting compound, in particular the complex.

In step (iva) according to this second alternative, the solution is preferably evaporated to dryness at elevated temperatures such as >room temperature to 50° C., more preferably 30 to 40° C.

Preferably, in step (va) the solvent or solvent mixture employed is a solvent in which the ARB and the NEPi in the complexed form exhibit a lower solubility that allows the dual-acting compound, in particular the complex to precipitate. Preferred solvents include the ones mentioned above for step (i), such as water, ethanol, 2-propanol, acetone ethylacetate, isopropyl acetate, methyl-t-butylether, acetonitrile, toluene, and methylene chloride and mixtures of such solvents, more preferably isopropyl acetate. Preferably, a minimum amount of solvent or solvent mixture is employed to facilitate precipitation.

In step (via) precipitation can take place at room temperature. It can be effected by leaving the mixture standing or by agitating the mixture, preferably by agitating it. This is preferably effected by stirring and/or sonication. After precipitation, the solid is collected, e.g. by filtration, and is dried to obtain the compound in accordance with the present invention. The drying step can be performed at room temperature or elevated temperature such as 30 to 60° C., preferably room temperature. Reduced pressure can be employed to facilitate removal of the solvent, preferably, drying is effected at ambient pressure.

In a fourth aspect, this invention is directed to a method of treating or preventing a disease or condition, such as hypertension, heart failure (acute and chronic) congestive heart failure, left ventricular dysfunction and hypertrophic cardiomyopathy, diabetic cardiac myopathy, supraventricular and ventricular arrhythmias, atrial fibrillation, atrial flutter, detrimental vascular remodeling, myocardial infarction and its sequelae, atherosclerosis, angina (unstable or stable), renal insufficiency (diabetic and non-diabetic), heart failure, angina pectoris, diabetes, secondary aldosteronism, primary and secondary pulmonary hypertension, renal failure conditions, such as diabetic nephropathy, glomerulonephritis, scleroderma, glomerular sclerosis, proteinuria of primary renal disease, and also renal vascular hypertension, diabetic retinopathy, other vascular disorders, such as migraine, peripheral vascular disease, Raynaud's disease, luminal hyperplasia, cognitive dysfunction (such as Alzheimer's), glaucoma and stroke comprising administering the afore-mentioned combination, linked pro-drug or the dual-acting compound, in particular the complex to a subject in need of such treatment.

The combination, linked pro-drug or the dual-acting compound, in particular the complex of the first embodiment may be administered alone or in the form of a pharmaceutical composition according to the second embodiment. Information regarding dosing, i.e., the therapeutically effective amount, etc., is the same regardless of how the combination, linked pro-drug or the dual-acting compound, in particular the complex is administered.

The combination, linked pro-drug or the dual-acting compound, in particular the complex is beneficial over a combination of ARBs or neutral endopeptidase inhibitors alone or other ARB/NEPi combinations with regard to use as first line therapy, ease of formulation and ease of manufacture.

Specific embodiments of the invention will now be demonstrated by reference to the following examples. It should be understood that these examples are disclosed solely by way of illustrating the invention and should not be taken in any way to limit the scope of the present invention.

Example 1

Preparation of [valsartan((2R,4S)-5-biphenyl4-yl-5-(3-carboxy-propionylamino)-2-methyl-pentanoic acid ethyl ester]$Na_3.2.5H_2O$

The dual-acting compound of valsartan and (2R,4S)-5-biphenyl4-yl-5-(3-carboxy-propionylamino)-2-methyl-pentanoic acid ethyl ester is prepared by dissolving 0.42 g of (2R,4S)-5-biphenyl4-yl-5-(3-carboxy-propionylamino)-2-methyl-pentanoic acid ethyl ester free acid (~95% purity) and 0.41 g of valsartan free acid in 40 ml acetone. Separately, 0.111 g of NaOH are dissolved in 7 ml H_2O. The two solutions are combined and stirred at room temperature for 1 hour and a clear solution was obtained. The solution is evaporated at 35° C. to yield a glassy solid. The glassy solid residue is then charged with 40 ml acetone and the resulting mixture is stirred and sonicated until precipitation occurred (~5 minutes). The precipitate was filtered and the solid is dried at room temperature in open air for 2 days until a constant mass of the crystalline solid is obtained.

Characterization by various methods could confirm the presence of both valsartan and (2R,4S)-5-biphenyl4-yl-5-(3-carboxy-propionylamino)-2-methyl-pentanoic acid ethyl ester and complex formation in contrast to a simple physical mixture. Significant spectral peaks for the complex are observed e.g. in the XRPD, IR, and Raman spectroscopy which are not present for the physical mixture. See below for details on the characterization.

Example 2

Alternative Preparation of [valsartan((2R,4S)-5-biphenyl4-yl-5-(3-carboxy-propionylamino)-2-methyl-pentanoic acid ethyl ester]$Na_3.2.5H_2O$

The dual acting compound of valsartan and (2R,4S)-5-biphenyl4-yl-5-(3-carboxy-propionylamino)-2-methyl-pentanoic acid ethyl ester is prepared by dissolving 22.96 mmol of (2R,4S)-5-biphenyl4-yl-5-(3-carboxy-propionylamino)-2-methyl-pentanoic acid ethyl ester free acid (~95% purity) and valsartan (10.00 g; 22.96 mmol) in acetone (300 mL). The suspension is stirred at room temperature for 15 min to obtain a clear solution. A solution of NaOH (2.76 g; 68.90 mmol) in water (8 mL) water is then added to this solution over a period of 10 min. Solids start to precipitate in 10 min. Alternatively, precipitation can be induced by seeding. The suspension is stirred at 20-25° C. for 2 h. This suspension is concentrated at 15-30° C. under reduced pressure (180-250 mbar) to a batch volume of ~150 mL. Isopropyl acetate (150 mL) is then added to the batch and the suspension is concentrated again at 15-30° C. under reduced pressure (180-250 mbar) to a batch volume of ~150 mL. This operation (addition of 150 mL of isopropyl acetate to the batch and concentration) is repeated once again. The suspension is stirred at 20-25° C. for 1 h. The solids are collected by filtration under nitrogen over a Büchner funnel, washed with isopropyl acetate (20 mL), and dried at 35° C. under reduced pressure (20 mbar) to afford the compound.

Characterization revealed the same product as in Example 1.

Example 3

Alternative Preparation of [valsartan((2R,4S)-5-biphenyl4-yl-5-(3-carboxy-propionylamino)-2-methyl-pentanoic acid ethyl ester]$Na_3.2.5H_2O$ using seeding

A reactor is charged with 2.00 kg (2,323 mmol) of AHU377 calcium salt and 20 L of isopropyl acetate. The suspension is stirred at 23±3° C., and 4.56 L of 2N HCl was added. The mixture is stirred at 23±3° C. for 15 min to obtain a clear two-phase solution. The organic layer is separated and washed with 3×4.00 L of water. The organic layer is concentrated at 30-100 mbar and 22±5° C. to ~3.5 L (3.47 kg) of AHU377 free acid isopropyl acetate solution as a colorless solution.

To the above reactor containing ~3.5 L (3.47 kg) of AHU377 free acid isopropyl acetate solution is added 1.984 kg (4,556 mmol) of Valsartan and 40 L of acetone. The reaction mixture is stirred at 23±3° C. to obtain a clear solution which is filtered into a reactor. To the reaction mixture is added a solution of 547.6 g (13,690 mmol) of NaOH in 1.0 L of water at 23±3° C. (which was pre-cooled to 20±5° C. and in-line filtered) over a period of 15-30 min while maintaining the internal temperature at 20-28° C. (slightly exothermic). The flask is rinsed with 190 mL of water and added into the reaction mixture. The reaction mixture is stirred at 23±3° C. for 15 min and a slurry of 4.0 g of [valsartan((2R,4S)-5-biphenyl4-yl-5-(3-carboxy-propionylamino)-2-methyl-pentanoic acid ethyl ester]$Na_3.2.5H_2O$ seeds in 50 mL of isopropyl acetate is added. The mixture is stirred at 23±3° C. for 2 h to obtain a suspension. The suspension is heated to an internal temperature at 40±3° C. over a period of 20 min and 20 L of isopropyl acetate is added over a period of 20 min while maintaining the internal temperature at 40±3° C. The suspension is stirred at this temperature for an additional 30 min. The mixture is concentrated at an internal temperature at 35±5° C. (T_j 45±5° C.) under reduced pressure (200-350 mbar) to ~35 L of a white slurry (solvent collected: ~25 L). Then 30 L of isopropyl acetate is added the mixture is concentrated at an internal temperature at 35±5° C. (T_j 45±5° C.) under reduced pressure (100-250 mbar) to ~30 L of a white slurry (solvent collected: ~40 L). Again 40 L of isopropyl acetate is added and the mixture is concentrated at an internal temperature at 35±5° C. (T_j 45±5° C.) under reduced pressure (100-200 mbar) to ~30 L of a white slurry (solvent collected: ~30 L). The reaction mixture is cooled to 23±3° C. over ~20 min and stirred at this temperature for an additional 3 h. The solid is collected by filtration under nitrogen over a polypropylene pad on Büchner funnel. The solid is washed with 2×5 L of isopropyl acetate and dried at 35° C. under reduced pressure (20 mbar) until isopropyl acetate content <0.5% to afford the above product as a white solid.

Characterization revealed the same product as in Example 1.

X-Ray Powder Diffraction

Calculation of the interlattice plane intervals from the X-ray powder pattern taken with a Scintag XDS2000 powder diffractometer for the most important lines for the sample give the following results:

d in [Å]: 21.2(s), 17.0(w), 7.1(s), 5.2(w), 4.7(w), 4.6(w), 4.2(w), 3.5(w), 3.3(w)

The error margin for all interlattice plane intervals is ±0.1 Å. The intensities of the peaks are indicated as follows: (w)=weak; (m)=medium; and (st)=strong.

Average values 2θ in [°] are indicated (error limit of ±0.2)

4.5, 5.5, 5.6, 9.9, 12.8, 15.7, 17.0, 17.1, 17.2, 18.3, 18.5, 19.8, 21.5, 21.7, 23.2, 23.3, 24.9, 25.3, 27.4, 27.9, 28.0, 30.2.

Elemental Analysis

Elemental analysis gives the following measured values of the elements present in the sample. The findings of the elemental analysis, within the error limits, correspond to the overall formula of $(C_{48}H_{55}N_6O_8Na_3).2.5H_2O$

Found	C: 60.05%	H: 6.24%	N: 8.80%
Calculated*	C: 60.18%	H: 6.31%	N: 8.77%

Infrared Spectroscopy

The infrared absorption spectrum for the sample obtained using Attenuated Total Reflection Fourier Transform Infrared (ATR-FTIR) spectrometer (Nicolet Magna-IR 560) shows the following significant bands, expressed in reciprocal wave numbers (cm^{-1}):

2956 (w), 1711 (st), 1637 (st), 1597 (st), 1488 (w), 1459 (m), 1401 (st), 1357 (w), 1295 (m), 1266 (m), 1176 (w), 1085 (m), 1010 (w), 1942(w), 907 (w), 862 (w), 763 (st), 742 (m), 698 (m), 533 (st).

The error margin for all absorption bands of ATR-IR is ±2 cm^{-1}.

The intensities of the absorption bands are indicated as follows: (w)=weak; (m)=medium; and (st)=strong intensity.

Raman Spectroscopy

Raman spectrum of the sample measured by dispersive Raman spectrometer with 785 nm laser excitation source (Kaiser Optical Systems, Inc.) shows the following significant bands expressed in reciprocal wave numbers (cm^{-1}):

3061 (m), 2930 (m, broad), 1612 (st), 1523 (m), 1461 (w), 1427 (w), 1287 (st), 1195 (w), 1108 (w), 11053 (w), 1041 (w), 1011 (w), 997 (m), 866(w), 850 (w), 822 (w), 808 (w), 735 (w), 715 (w), 669 (w), 643 (w), 631 (w), 618 (w), 602 (w), 557 (w), 522 (w), 453 (w), 410 (w), 328 (w).

The error margin for all Raman bands is ±2 cm^{-1}.

The intensities of the absorption bands are indicated as follows: (w)=weak; (m)=medium; and (st)=strong intensity.

High Resolution CP-MAS ^{13}C NMR Spectroscopy

The samples are investigated by high resolution CP-MAS (Cross Polarization Magic Angle Spinning) ^{13}C NMR spectroscopy using a Bruker-BioSpin AVANCE 500 NMR spectrometer equipped with a 300 Watt high power ^{1}H, two 500 Watt high power X-amplifiers, necessary high power preamplifiers, a "MAS" controller and a 4 mm BioSolids high resolution Bruker probe.

Each sample is packed in a 4 mm ZrO_2 rotor. Critical experimental parameters are 3 msec ^{13}C contact times, 12 KHz spinning speed at the magic angle, a "ramped" contact time, using a "SPINAL64" ^{1}H decoupling scheme, a recycle delay of 10 secs and 1024 scans at 293 deg K. The chemical shifts are referenced with respect to an external Glycine carbonyl at 176.04 ppm.

High resolution CP-MAS ^{13}C NMR shows the following significant peaks (ppm):

179.0, 177.9 177.0, 176.7, 162.0, 141.0, 137.2, 129.6, 129.1, 126.7, 125.3, 64.0, 61.5, 60.4, 50.2, 46.4, 40.6, 38.6, 33.5, 32.4, 29.8, 28.7, 22.3, 20.2, 19.1, 17.8, 16.8, 13.1, 12.1, 11.1.

A physical mixture of individual Na salts of Valsartan and (2R,4S)-5-biphenyl4-yl-5-(3-carboxy-propionylamino)-2-methyl-pentanoic acid ethyl ester revealed a simple inert mixture of the two salts. However, the sample of the complex prepared in Example 1 exhibited distinctly different spectral features in comparison to a 1:1 mixture of the sodium salts.

DSC and TGA

As measured by differential scanning calorimetry (DSC) using Q1000 (TA Instruments) instrument, the melting onset temperature and the peak maximum temperature for the sample is observed at 139° C. and 145° C., respectively.

As shown by DSC and thermogravimetric analysis (TGA), upon heating, the water of hydration is released in two steps: the first step occurs below 100° C. and the second step above 120° C.

Both DSC and TGA instruments are operated at a heating rate of 10 K/min.

Example 4

Preparation of Linked Pro-Drug of Scheme (1)

Linked pro-drug of valsartan calcium salt and (2R,4S)-5-biphenyl4-yl-5-(3-carboxy-propionylamino)-2-methyl-pentanoic acid ethyl ester is prepared at room temperature by dissolving 114 mg of the calcium salt of valsartan and 86 mg of (2R,4S)-5-biphenyl4-yl-5-(3-carboxy-propionylamino)-2-methyl-pentanoic acid ethyl ester free acid in 2 mL methanol, followed by methanol evaporation. The glassy solid residue is then charged with 3 mL of acetonitrile and equilibrated by 10 min. sonication, followed by 20 hours of magnetic stirring.

Approximately 120 mg of white solids are collected by filtration. Liquid chromatography (LC) and elemental analysis indicate 1:1 ratio between (2R,4S)-5-biphenyl4-yl-5-(3-carboxy-propionylamino)-2-methyl-pentanoic acid ethyl ester and valsartan. The sample is amorphous by X-ray powder diffraction.

Preparation of Linked Pro-Drug of Scheme (2)

Linked pro-drug of valsartan calcium salt and (2R,4S)-5-biphenyl4-yl-5-(3-carboxy-propionylamino)-2-methyl-pentanoic acid ethyl ester and Tris is prepared at room temperature by dissolving 57 mg of the calcium salt of valsartan, 43 mg of (2R,4S)-5-biphenyl4-yl-5-(3-carboxy-propionylamino)-2-methyl-pentanoic acid ethyl ester free acid, and 12.6 mg of tris(hydroxymethyl)aminomethane (Tris) in 2 mL methanol, followed by methanol evaporation. The glassy solid residue is then charged with 3 mL of acetonitrile and equilibrated by 10 min. sonication, followed by 20 hours of magnetic stirring. Approximately 83 mg of white solids are collected by filtration. LC and elemental analysis indicate 1:1 ratio between (2R,4S)-5-biphenyl4-yl-5-(3-carboxy-propionylamino)-2-methyl-pentanoic acid ethyl ester and valsartan. The sample is amorphous by X-ray powder diffraction.

While the invention has been described above with reference to specific embodiments thereof, it is apparent that many changes, modifications, and variations can be made without departing from the inventive concept disclosed herein. Accordingly, it is intended to embrace all such changes, modifications and variations that fall within the spirit and broad scope of the appended claims. All patent applications, patents, and other publications cited herein are incorporated by reference in their entirety.

What is claimed is:

1. A method for treatment of a cardiovascular condition or disease, wherein the cardiovascular condition or disease is heart failure or hypertension, in a patient in need thereof comprising administering to the patient a therapeutically effective amount of trisodium[3-((1S,3R)-1-biphenyl-4-ylmethyl-3-ethoxycarbonyl-1-butylcarbamoyl)propionate-(S)-3'-methyl-2'-(pentanoyl{2"-(tetrazol-5-ylate)biphenyl-4'-ylmethyl}amino)butyrate]hemipentahydrate.

2. The method according to claim **1**, wherein the heart failure is chronic heart failure.

3. The method according to claim **1**, wherein the condition or disease is hypertension.

4. The method according to claim 1, wherein the compound trisodium[3-((1S,3R)-1-biphenyl-4-ylmethyl-3-ethoxycarbonyl-1-butylcarbamoyl)propionate-(S)-3'-methyl-2'-(pentanoyl{2"-(tetrazol-5-ylate)biphenyl-4'-ylmethyl}amino)butyrate]hemipentahydrate is administered in the form of a pharmaceutical composition.

5. The method according to claim 1, wherein the compound trisodium[3-((1S,3R)-1-biphenyl-4-ylmethyl-3-ethoxycarbonyl-1-butylcarbamoyl)propionate-(S)-3'-methyl-2'-(pentanoyl{2"-(tetrazol-5-ylate)biphenyl-4'-ylmethyl}amino)butyrate]hemipentahydrate is in the crystalline form.

6. The method according to claim 5, wherein the compound trisodium[3-((1S,3R)-1-biphenyl-4-ylmethyl-3-ethoxycarbonyl-1-butylcarbamoyl)propionate-(S)-3'-methyl-2'-(pentanoyl{2"-(tetrazol-5-ylate)biphenyl-4'-ylmethyl}amino)butyrate]hemipentahydrate is characterized by an Attenuated Total Reflection Fourier Transform Infrared (ATR-FTIR) spectrum having the following absorption bands expressed in reciprocal wave numbers (cm−1)(±2 cm−1): 1711 (st), 1637 (st), 1597 (st) and 1401 (st).

7. The method according to claim 5, wherein the compound trisodium[3-((1S,3R)-1-biphenyl-4-ylmethyl-3-ethoxycarbonyl-1-butylcarbamoyl)propionate-(S)-3'-methyl-2'-(pentanoyl{2"-(tetrazol-5-ylate)biphenyl-4'-ylmethyl}amino)butyrate]hemipentahydrate is characterized by an Attenuated Total Reflection Fourier Transform Infrared (ATR-FTIR) spectrum having the following absorption bands expressed in reciprocal wave numbers (cm−1)(±2 cm−1): 2956 (w), 1711 (st), 1637 (st), 1597 (st), 1488 (w), 1459 (m), 1401 (st), 1357 (w), 1295 (m), 1266 (m), 1176 (w), 1085 (m), 1010 (w), 942(w), 907 (w), 862 (w), 763 (st), 742 (m), 698 (m), 533 (st).

8. The method according to claim 5, wherein the compound trisodium[3-((1S,3R)-1-biphenyl-4-ylmethyl-3-ethoxycarbonyl-1-butylcarbamoyl)propionate-(S)-3'-methyl-2'-(pentanoyl{2"-(tetrazol-5-ylate)biphenyl-4'-ylmethyl}amino)butyrate]hemipentahydrate is characterized by an X-ray powder diffraction pattern taken with a Scintag XDS2000 powder diffractometer comprising the following interlattice plane intervals:

d in [Å] (±0.1 Å): 21.2(s), 17.0(w), 7.1(s), 5.2(w), 4.7(w), 4.6(w), 4.2(w), 3.5(w), 3.3(w).

9. The method according to claim 5, wherein the compound trisodium[3-((1S,3R)-1-biphenyl-4-ylmethyl-3-ethoxycarbonyl-1-butylcarbamoyl)propionate-(S)-3'-methyl-2'-(pentanoyl{2"-(tetrazol-5-ylate)biphenyl-4'-ylmethyl}amino)butyrate]hemipentahydrate is characterized by an X-ray powder diffraction pattern taken with a Scintag XDS2000 powder diffractometer comprising the following interlattice plane intervals, 2θ in [°]) (±0.2°) 4.5, 5.5, 5.6, 9.9, 12.8, 15.7, 17.0, 17.1, 17.2, 18.3, 18.5, 19.8, 21.5, 21.7, 23.2, 23.3, 24.9, 25.3, 27.4, 27.9, 28.0, 30.2.

10. The method according to claim 5, wherein the compound trisodium[3-((1S,3R)-1-biphenyl-4-ylmethyl-3-ethoxycarbonyl-1-butylcarbamoyl)propionate-(S)-3'-methyl-2'-(pentanoyl{2"-(tetrazol-5-ylate)biphenyl-4'-ylmethyl}amino)butyrate]hemipentahydrate is in the form of a monoclinic unit cell, wherein its cell content comprises twelve formula units of C48H55N6O8Na3.2.5H2O.

11. The method according to claim 10, wherein the compound trisodium[3-((1S,3R)-1-biphenyl-4-ylmethyl-3-ethoxycarbonyl-1-butylcarbamoyl)propionate-(S)-3'-methyl-2'-(pentanoyl{2"-(tetrazol-5-ylate)biphenyl-4'-ylmethyl}amino)butyrate]hemipentahydrate is in the form of a monoclinic unit cell, wherein the cell content of the monoclinic unit cell comprises two asymmetric units on two-fold positions.

12. The method according to claim 10, wherein the monoclinic unit cell has a P2i space group.

13. The method according to claim 5, wherein the compound trisodium[3-((1S,3R)-1-biphenyl-4-ylmethyl-3-ethoxycarbonyl-1-butylcarbamoyl)propionate-(S)-3'-methyl-2'-(pentanoyl{2"-(tetrazol-5-ylate)biphenyl-4'-ylmethyl}amino)butyrate]hemipentahydrate is characterized by

sum formula C48H55N6O8Na3.2.5H2O
molecular mass 957.99
crystal colour colourless
crystal shape tabular: hexagonal
crystal system monoclinic
space group P21
Cell parameters
a=20.344 Å
b=42.018 Å
c=20.374 Å
α=90 0
β=119.29
γ=90 o
volume of unit cell 15190.03 Å3
Z (the number of asymmetric units in the unit cell) 2
calculated density 1.26845 g/cm3.

14. The method according to claim 5, wherein the compound trisodium[3-((1S,3R)-1-biphenyl-4-ylmethyl-3-ethoxycarbonyl-1-butylcarbamoyl)propionate-(S)-3'-methyl-2'-(pentanoyl{2"-(tetrazol-5-ylate)biphenyl-4'-ylmethyl}amino)butyrate]hemipentahydrate has the sum formula C48H55N6O8Na3.2.5H2O and is in the form of an asymmetric unit comprising six C48H55N6O8Na3.2.5H2O formula units.

15. The method according to claim 5, wherein the compound trisodium[3-((1S,3R)-1-biphenyl-4-ylmethyl-3-ethoxycarbonyl-1-butylcarbamoyl)propionate-(S)-3'-methyl-2'-(pentanoyl{2"-(tetrazol-5-ylate)biphenyl-4'-ylmethyl}amino)butyrate]hemipentahydrate is characterized by an X-ray powder diffraction pattern taken with a Scintag XDS2000 powder diffractometer comprising the following interlattice plane intervals, 2e in [°]) (±0.2°) 4.5, 5.6, 12.8, 17.0, 17.2, 19.8, 21.5, 27.4.

* * * * *

UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

PATENT NO. : 9,388,134 B2
APPLICATION NO. : 14/311788
DATED : July 12, 2016
INVENTOR(S) : Lili Feng et al.

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

In the Specification

Column 11:
Lines 20-22, "(2R,4S)-5-biphenyl4-yl-5-(3-carboxy-propionylamino)-2-methyl-pentanoic acid ethyl ester"
Should read:
--(2R,4S)-5-biphenyl-4-yl-4-(3-carboxy-propionylamino)-2-methyl-pentanoic acid ethyl ester--.

Column 12:
Lines 21-22, "5-biphenyl4-yl-5-(3-carboxy-propionylamino)-2-methyl-pentanoic acid ethyl ester"
Should read:
--5-biphenyl-4-yl-4-(3-carboxy-propionylamino)-2-methyl-pentanoic acid ethyl ester--;
Lines 23-24, "5-biphenyl4-yl-5-(3-carboxy-propionylamino)-2-methyl-pentanoic acid"
Should read:
--5-biphenyl-4-yl-4-(3-carboxy-propionylamino)-2-methyl-pentanoic acid--; and
Lines 43-45, "(2R,4S)-5-biphenyl4-yl-5-(3-carboxy-propionylamino)-2-methyl-pentanoic acid ethyl ester"
Should read:
--(2R,4S)-5-biphenyl-4-yl-4-(3-carboxy-propionylamino)-2-methyl-pentanoic acid ethyl ester--.

Column 14:
Lines 24-25, "(2R,4S)-5-biphenyl4-yl-5-(3-carboxy-propionylamino)-2-methyl-pentanoic acid ethyl ester"
Should read:
--(2R,4S)-5-biphenyl-4-yl-4-(3-carboxy-propionylamino)-2-methyl-pentanoic acid ethyl ester--; and
Lines 65-66, "[valsartan((2R,4S)-5-biphenyl4-yl-5-(3-carboxy-propionylamino)-2-methyl-pentanoic acid ethyl ester]$Na_3.xH_2O$"
Should read:
--[3-((1S,3R)-1-biphenyl-4-ylmethyl-3-ethoxycarbonyl-1-butylcarbamoyl)propionate-(S)-3'-methyl-2'-(pentanoyl{2"-(tetrazol-5-ylate)biphenyl-4'ylmethyl}amino)butyrate]$Na_3 \cdot xH_2O$--.

Signed and Sealed this
Twenty-ninth Day of October, 2019

Andrei Iancu
Director of the United States Patent and Trademark Office

Column 15:
Lines 9-10, "(5-biphenyl4-yl-5-(3-carboxy-propionylamino)-2-methyl-pentanoic acid ethyl ester]"
Should read:
--(5-biphenyl-4-yl-4-(3-carboxy-propionylamino)-2-methyl-pentanoic acid ethyl ester)]--; and
Lines 12-14, "((2R,4S)-5-biphenyl4-yl-5-(3-carboxy-propionylamino)-2-methyl-pentanoic acid ethyl ester]"
Should read:
--((2R,4S)-5-biphenyl-4-yl-4-(3-carboxy-propionylamino)-2-methyl-pentanoic acid ethyl ester)]--.

Column 16:
Lines 9-11, "(2R,4S)-5-biphenyl4-yl-5-(3-carboxy-propionylamino)-2-methyl-pentanoic acid ethyl ester"
Should read:
--(2R,4S)-5-biphenyl-4-yl-4-(3-carboxy-propionylamino)-2-methyl-pentanoic acid ethyl ester--.

Column 19:
Line 27, "1942(w)"
Should read:
--942(w)--.

Column 27:
Lines 3-5, "[valsartan((2R,4S)-5-biphenyl4-yl-5-(3-carboxy-propionylamino)-2-methyl-pentanoic acid ethyl ester]$Na_3.2.5H_2O$"
Should read:
--Trisodium [3-((1S,3R)-1-biphenyl-4-ylmethyl-3-ethoxycarbonyl-1-butylcarbamoyl)propionate-(S)-3'-methyl-2'-(pentanoyl{2"-(tetrazol-5-ylate)biphenyl-4'-ylmethyl}amino)butyrate] hemipentahydrate--;
Lines 7-9, "of valsartan and (2R,4S)-5-biphenyl4-yl-5-(3-carboxy-propionylamino)-2-methyl-pentanoic acid ethyl ester"
Should read:
--Trisodium [3-((1S,3R)-1-biphenyl-4-ylmethyl-3-ethoxycarbonyl-1-butylcarbamoyl)propionate-(S)-3'-methyl-2'-(pentanoyl{2"-(tetrazol-5-ylate)biphenyl-4'-ylmethyl}amino)butyrate] hemipentahydrate--;
Lines 10-11, "(2R,4S)-5-biphenyl4-yl-5-(3-carboxy-propionylamino)-2-methyl-pentanoic acid ethyl ester"
Should read:
--(2R,4S)-5-biphenyl-4-yl-4-(3-carboxy-propionylamino)-2-methyl-pentanoic acid ethyl ester--;
Lines 22-24, "(2R,4S)-5-biphenyl4-yl-5-(3-carboxy-propionylamino)-2-methyl-pentanoic acid ethyl ester"
Should read:
--(2R,4S)-5-biphenyl-4-yl-4-(3-carboxy-propionylamino)-2-methyl-pentanoic acid ethyl ester--;
Lines 31-33, "[valsartan((2R,4S)-5-biphenyl4-yl-5-(3-carboxy-propionylamino)-2-methyl-pentanoic acid ethyl ester]$Na_3.2.5H_2O$"
Should read:
--Trisodium [3-((1S,3R)-1-biphenyl-4-ylmethyl-3-ethoxycarbonyl-1-butylcarbamoyl)propionate-(S)-3'-methyl-2'-(pentanoyl{2"-(tetrazol-5-

ylate)biphenyl-4'-ylmethyl}amino)butyrate] hemipentahydrate--;
Lines 35-37, "of valsartan and (2R,4S)-5-biphenyl4-yl-5-(3-carboxy-propionylamino)-2-methyl-pentanoic acid ethyl ester"
Should read:
--Trisodium [3-((1S,3R)-1-biphenyl-4-ylmethyl-3-ethoxycarbonyl-1-butylcarbamoyl)propionate-(S)-3'-methyl-2'-(pentanoyl{2"-(tetrazol-5-ylate)biphenyl-4'-ylmethyl}amino)butyrate] hemipentahydrate--;
Lines 38-39, "(2R,4S)-5-biphenyl4-yl-5-(3-carboxy-propionylamino)-2-methyl-pentanoic acid ethyl ester"
Should read:
--(2R,4S)-5-biphenyl-4-yl-4-(3-carboxy-propionylamino)-2-methyl-pentanoic acid ethyl ester--; and
Lines 62-64, "[valsartan((2R,4S)-5-biphenyl4-yl-5-(3-carboxy-propionylamino)-2-methyl-pentanoic acid ethyl ester]$Na_3.2.5H_2O$"
Should read:
--Trisodium [3-((1S,3R)-1-biphenyl-4-ylmethyl-3-ethoxycarbonyl-1-butylcarbamoyl)propionate-(S)-3'-methyl-2'-(pentanoyl{2"-(tetrazol-5-ylate)biphenyl-4'-ylmethyl}amino)butyrate] hemipentahydrate--.

Column 28:
Lines 20-22, "[valsartan((2R,4S)-5-biphenyl4-yl-5-(3-carboxy-propionylamino)-2-methyl-pentanoic acid ethyl ester]$Na_3.2.5H_2O$"
Should read:
--Trisodium [3-((1S,3R)-1-biphenyl-4-ylmethyl-3-ethoxycarbonyl-1-butylcarbamoyl)propionate-(S)-3'-methyl-2'-(pentanoyl{2"-(tetrazol-5-ylate)biphenyl-4'-ylmethyl}amino)butyrate] hemipentahydrate--.

Column 29:
Line 13, "1942(w)"
Should read:
--942(w)--; and
Lines 56-57, "(2R,4S)-5-biphenyl4-yl-5-(3-carboxy-propionylamino)-2-methyl-pentanoic acid ethyl ester"
Should read:
--(2R,4S)-5-biphenyl-4-yl-4-(3-carboxy-propionylamino)-2-methyl-pentanoic acid ethyl ester--.

Column 30:
Lines 12-14, "(2R,4S)-5-biphenyl4-yl-5-(3-carboxy-propionylamino)-2-methyl-pentanoic acid ethyl ester"
Should read:
--(2R,4S)-5-biphenyl-4-yl-4-(3-carboxy-propionylamino)-2-methyl-pentanoic acid ethyl ester--;
Lines 16-17, "(2R,4S)-5-biphenyl4-yl-5-(3-carboxy-propionylamino)-2-methyl-pentanoic acid ethyl ester"
Should read:
--(2R,4S)-5-biphenyl-4-yl-4-(3-carboxy-propionylamino)-2-methyl-pentanoic acid ethyl ester--;
Lines 24-26, "(2R,4S)-5-biphenyl4-yl-5-(3-carboxy-propionylamino)-2-methyl-pentanoic acid ethyl ester"

Should read:
--(2R,4S)-5-biphenyl-4-yl-4-(3-carboxy-propionylamino)-2-methyl-pentanoic acid ethyl ester--;
Lines 31-33, "(2R,4S)-5-biphenyl4-yl-5-(3-carboxy-propionylamino)-2-methyl-pentanoic acid ethyl ester"
Should read:
--(2R,4S)-5-biphenyl-4-yl-4-(3-carboxy-propionylamino)-2-methyl-pentanoic acid ethyl ester--;
Lines 35-36, "(2R,4S)-5-biphenyl4-yl-5-(3-carboxy-propionylamino)-2-methyl-pentanoic acid ethyl ester"
Should read:
--(2R,4S)-5-biphenyl-4-yl-4-(3-carboxy-propionylamino)-2-methyl-pentanoic acid ethyl ester--; and
Lines 43-44, "(2R,4S)-5-biphenyl4-yl-5-(3-carboxy-propionylamino)-2-methyl-pentanoic acid ethyl ester"
Should read:
--(2R,4S)-5-biphenyl-4-yl-4-(3-carboxy-propionylamino)-2-methyl-pentanoic acid ethyl ester--.

In the Claims

Column 32:
Line 14, Claim 12 "P2i"
Should read:
--$P2_1$--;
Line 26, Claim 13 "P21"
Should read:
--$P2_1$--.